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Nocardiose Oculaire Endogène

THESE

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(avec la co-direction du Docteur Yan Guex-Crosier)

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par

Margherita ESCHLE-MENICONI

Médecin diplômé de la Confédération Suisse
Originaire de Zurich

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Nocardiose Oculaire Endogène

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Nocardiose oculaire endogène

Publication d'un cas avec revue systématique de la littérature

Introduction

Nous avons diagnostiqué et traité un patient atteint de nocardiose oculaire endogène. Grâce à la chirurgie vitréo-rétinienne, le diagnostique définitif a pu être établi avec un résultat oculaire fonctionnel excellent. La nocardiose oculaire endogène étant une maladie rare, l'image clinique oculaire et la prise en charge n'ont pas encore été décrites systématiquement. Nous avons analysé tous les cas rapportés dans la littérature mondiale (38 cas, publiés jusqu'en 2007) pour trouver des indices sur la physiopathologie, la présentation oculaire, sur la meilleure façon d'établir le diagnostique et sur l'efficacité du traitement antibiotique systémique. Enfin, nous avons établit des directives pour la prise en charge oculaire.

La nocardiose (défini comme maladie systémique ou locale) est une maladie touchant surtout des patients immunosupprimés ou immunocompromis comme les patients transplantés, avec maladie auto-immune, atteints du virus HIV sans HAART ou des patients ayant subit un trauma, une opération avec inoculation du germe. Aux Etats-Unis environs 500-1000 nouveaux cas sont diagnostiqués par année avec 20% de dissémination dans des autres organes, le plus fréquemment dans le cerveau. Environs 0.6-1% des patients (3-5 cas/année/US) auront un foyer dans l'œil, c'est-à-dire la nocardiose oculaire endogène. *Nocarida* est un Actinomycète, classé comme bactérie, avec une morphologie et un comportement proche aux champignons, avec un cycle de reproduction lente, se trouvant dans la poussière (ubiquitaire) et la matière végétale se décomposant. Elle est sensible aux sulfamides avec émergence de résistances. La mortalité est environs de 25%.

Résultats

La moitié des patients présentait comme premier signe de la maladie systémique des problèmes oculaires, le plus souvent une baisse d'acuité visuelle progressive indolore. Un abcès choroïdien unilatéral unique dans la région maculaire associé ou non à un décollement rétinien séreux et/ou à une vitrite variable était la présentation dans 70% des cas. *Nocardia* dissémine au niveau des choriocapillaires, rarement, dans l'iris résultant dans un hypopyon isolé. Il y a deux modes de propagation locale: vers l'intérieur, par une nécrose de l'épithélium pigmentaire avec l'envahissement de la rétine et du corps vitré; vers l'extérieure, produisant une sclérite résultant dans une perforation du globe. Avant la séquestration au niveau du corps vitré, la réponse au traitement par antibiose voie générale est favorable: 75% des cas analysés. La rupture de la barrière hémato-oculaire externe (épithélium pigmentaire) peut être mis en évidence par la fluorescence angiographique : les images tardives montrent la diffusion de la fluorescéine dans le corps vitré. Si le corps vitré est atteint, au minimum des injections antibiotiques intravitréen (amikacin), mieux une vitréctomie sont indiqué pour diminuer la charge bactérienne et faciliter la pénétration des antibiotiques donnés par voie systémique. Signes d'une extériorisation d'un abcès choroïdien sont des douleurs intenses, l'exophthalmie et l'hypopyon associé.

Soixante-deux pourcents des patients ont souffert d'une dissémination continue par retardement du diagnostique/traitement. La moitié des patients ont eu des abcès cérébraux avant, simultanément ou après présentation. Un quart des patients sont décédés suite de la nocardiose, 32% incluant la maladie de base (tumeur maligne hématologique) ou des autres infections opportunistiques (aspergillose). La morbidité oculaire est importante: un tiers des patients survivants ont retenu une acuité visuelle 0.5 ou mieux, un tiers une acuité visuelle égale ou inférieure à 0.1 et un tiers ont perdu l'œil par énucléation/éviscération(1).

La suspicion clinique et la biopsie de la lésion pour un examen microbiologique direct et des cultures sont cruciales pour la prise en charge. Les risques facteurs sont sexe masculin (4 :1), stéroïdes, immunosuppression pour transplantation ou maladie auto-immune et des tumeurs hématologiques malignes, plus rarement des accidents/ traumas graves. La ponction directe de la lésion assure les meilleures chances pour collectionner un spécimen contenant des bactéries: dans des petits abcès sous-rétiniens maculaires par ponction transvitréenne sous-rétinienne par aiguille fine décrit par le Prof. Augsburger (Référence 7) ou dans des lésions avancées par biopsie sous-rétinienne/rétinienne pendant une vitréctomie selon l'extension et la localisation de l'abcès. Le spécimen doit être préparé pour un examen direct (4 lames) et des cultures utilisant des plaques ordinaires sauf exceptions. La suspicion doit être communiquée au laboratoire et les cultures incubées de façon prolongée (4-6 semaines). Un bilan d'extension avec au minimum un CT scan thoracique et une IRM cérébrale sont indiqués.

Le traitement de choix est un antibiotique du groupe des sulfamides à haute dose comme par exemple le co-trimoxazole à double dose. Le choix, le nombre et le dosage du/des médicaments doivent être adapté selon résistance, extension de la maladie, médicaments autres et état de santé général du patient (foie, reins). Les figures 6a et 6b illustrent la prise en charge de patients selon diagnostique établit (Fig. 6b) ou non (Fig 6a).

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ELSEVIER

MAJOR REVIEW

Endogenous Ocular Nocardiosis—An Interventional Case Report With a Review of the Literature

Margherita E. Eschle-Meniconi, MD, Yan Guex-Crosier, MD, and Thomas J. Wolfensberger, MD

Jules Gonin Eye Hospital, University of Lausanne, Switzerland

Abstract. We present an illustrative case of endogenous ocular *Nocardia* (EON) infection in a man with Hodgkin disease treated by chemotherapy who underwent aggressive vitreoretinal surgery for diagnosis and treatment of a subretinal abscess. Visual acuity recovered from hand movements to 20/25. We review the 38 reported cases of EON published between 1967 and 2007, describe the clinical presentation from a systemic and ocular point of view, examine which ocular procedures were successful in identifying the bacterium, and analyze ocular morbidity and the factors affecting successful treatment. (**Surv Ophthalmol 56:**383–415, 2011. © 2011 Elsevier Inc. All rights reserved.)

Key words. amikacin • chorioretinal exudates • chorioretinitis • endogenous ocular *Nocardia* infection • endophthalmitis • hypopyon • nocardiosis • resistance • subretinal abscess • trimethoprim-sulfamethoxazole • uveitis

I. Introduction

About 5–10% of all endophthalmitis is endogenous. *Staphylococcus* sp., *Streptococcus* sp., *Escherichia coli*,[53] and *Candida* sp.[94] account for most. In a recent single-center, 10-year, retrospective study,[94] *Nocardia* sp. represented only 3% of endogenous endophthalmitis. *Nocardia* was identified as the most frequent bacterial and *Aspergillus* as the most frequent fungal cause of a subretinal abscess.[53] As the result of its slow growth and choroidal affinity, *Nocardia* endophthalmitis presents differently than other endogenous bacterial endophthalmitis.

Nocardia, an actinomycetale, is a fungus-like, filamentous, slow-cycling, aerobic, Gram-positive bacterium[119] with variable staining. A soil saprophyte, it is found in dust and decaying vegetable matter. Immunocompromized men are particularly vulnerable to infection. The incidence of nocardiosis, defined as local or systemic infection by *Nocardia*, in the United States was estimated in the 1980s to be between 500 and 1,000 cases per year. Eighty-five percent (85%) of patients have a serious pulmonary or systemic infection.[11] Spreading to distant sites occurs in about 20% of cases, the brain being the organ most affected (15%).[11] About 3–5% of those who have bacteremia will have a focus in the eye.[19] Thus, 0.6–1% of systemic nocardiosis is expected to develop endogenous ocular *Nocardia* (EON)—or about 3–10 cases/year in the United States. The clinical picture is highly variable. Since the introduction of sulfonamides, mortality has greatly decreased, from 80% to 25%. Visual morbidity, however, remains substantial. Lakosha et al[74] found that in exo- and endogenous ocular *Nocardia* infections, only 13% of eyes retained visual acuities of 20/40 or more.

We report a patient who presented with a subretinal abscess as the initial manifestation of

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disseminated nocardiosis. Aggressive vitreoretinal surgery established diagnosis and led to a good visual outcome.

Because of the rarity of disease, the management of EON is not standardized. We analyzed all cases of EON published in Medline journals from 1967 to 2007 in form of a retrospective case series. We describe clinical presentation, methods of diagnosis, treatment efficacy, and attempt to develop criteria for the management of EON.

II. Case Report

A 78-year-old man presented with a 2-week history of painless decreased vision in his left eye. His medical history was significant for an adenocarcinoma of the prostate treated by a transurethral resection of the prostate 7 months previously and for a Hodgkin lymphoma stage IV of the sclerosenodular type, diagnosed 2 months before presentation. At that time, he had lost 15 kg, was pancytopenic, and had hepatosplenomegaly with portal hypertension. He improved after a short course of high-dose steroids, followed by three reduced doses of chemotherapy AVBD (adriamycine, vinblastine, bleomycine, dacarbazine: the first and second cycles consisted of 50% of the total dose of adriamycine and vinblastine and 66% of the total dose of dacarbazine and bleomycine. During the third cycle all four agents were given at 66% of the total dosage). Chemotherapy resulted in a good clinical and biological response.

Upon presentation 2 weeks after the third cycle of chemotherapy, the patient was on 2.5 mg/day prednisone and weekly granulocyte colony-stimulation factor injections. Visual acuity was 20/20 in the right eye; he saw only hand movements in the left eye. Intraocular pressure was 13 mm Hg in the right eye and 6 mm Hg in the left eye. Both eyes were pseudophakic. The left anterior segment and vitreous contained a few cells. Funduscopic examination showed a yellow-white subretinal mass temporal to the macula. The right eye was normal.

The differential diagnosis included fungal endophthalmitis, metastasis of prostate adenocarcinoma, or Hodgkin infiltration. A vitreous tap was performed, but did not reveal any organisms (direct examination, culture, polymerase chain reaction [PCR] for bacteria and fungus) or malignant cells. Serologic work-up for *Toxoplasmosis, Bartonella henselae,* and HIV were negative. Three days later, the patient's general health deteriorated with fever (38.2C), neck stiffness, vertical gaze, and a left arm paresis, and he was admitted to neurology. Cardiovascular, pulmonary, abdominal, and laboratory exams were unchanged compared to post-chemotherapy studies: mild leucocytosis (12.6 G/L), hemoglobin at 115 g/L, decreased thrombocytes (114 G/L), and an elevated CRP (20 mg/L) that increased the following day to 65 mg/L. A brain computed tomography (CT) scan showed a round lesion measuring 1 cm in diameter at the left superior colliculus, and magnetic resonance imaging (MRI) detected six additional lesions distributed in both hemispheres with hypo-intense centers and annular enhancement. A lumbar puncture yielded cloudy cerebrospinal fluid (CSF) with 400 leucocytes/mm^3 (41% lymphocytes, 41% neutrophiles, 13.5% monocytes/macrophages, 3.5% plasmocytes, and 1% eosinophiles), no organism on smears, normal glucose, and increased total proteins (697 mg/L [normal, 150–460 mg/L]). A chest CT scan showed a condensation line not present on prior images in the left pulmonary apex compatible with infection or tumoral infiltration. A transthoracic echocardiogram was normal. A urinary tract infection was present. Intravenous ceftriaxone and clarithromycin were administrated, and prednisone was increased to 5 mg/day.

Despite this treatment, the patient's condition did not improve. On ophthalmic follow-up 1 week after the vitreous tap visual acuity was still hand movements. The conjunctiva, anterior chamber, and vitreous now were severely inflamed. There was leucocoria. The subretinal abscess (Fig. 1) was associated with new superficial retinal hemorrhages. Confronted with a multifocal disease

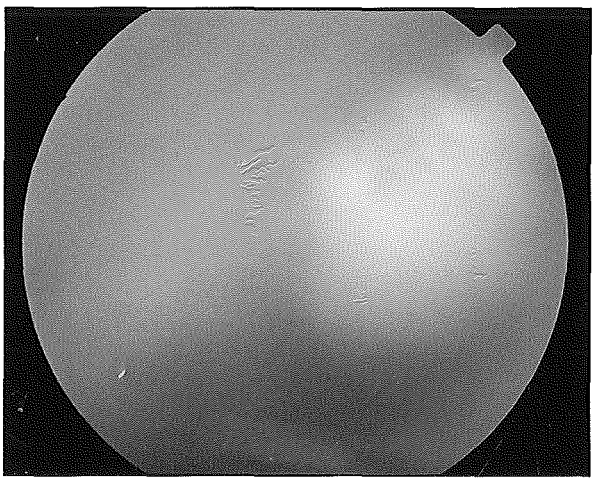

Fig. 1. Pre-operative picture of the left eye showing the peripheral temporal fundus with marked vitritis and a hazy yellow-white subretinal lesion with superficial hemorrhages. Visual acuity was hand movements.

without a clear diagnosis the eye was considered the most accessible site for diagnostic biopsy. Under local anesthesia a pars plana vitrectomy (PPV), a retinectomy of the peripheral temporal retina from the 2–5 o'clock position, and aspiration of the subretinal abscess was done. This was followed by endolaser under perfluorocarbon liquids and instillation of silicone oil. The suspicion of *Nocardia* was communicated to the microbiology laboratory. Examination of the subretinal material confirmed Gram-positive, branching filaments consistent with *Nocardia* (Figure 2). Four hours after surgery the patient received high doses of intravenous trimethoprim-sulfamethaxozole (TM-SMX; 10 mg/kg/day and 50 mg/kg/day). After a latency of 10 days, *Nocardia farcinica* grew in cultures of the subretinal abscess and in one of the two samples of CSF. Blood cultures and all vitreous samples remained negative. *N. farcinica* was sensitive to TM-SMX, meropenem, ciprofloxacin, and rifampicin and was resistant to erythromycin, clarithromycin, and clindamycin.

The general condition of the patient improved. No postoperative ocular complication occurred. Best-corrected visual acuity improved to counting fingers after 1 week, then to Snellen 20/600 in 2 weeks, and to 20/25 at 3.5 months. There was a choroidal scar in the region where the retinectomy had been performed; the macula and peripheral retina remained attached under silicone oil (Fig. 3).

Neurologically, the patient retained a memory deficit and a frontal lobe syndrome. Upon discharge, oral TM-SMX (Bactrim forte 1000 mg three times a day) and prednisone 5 mg/day were continued. No further chemotherapy was administered, and the patient died 4 months later from progressive Hodgkin lymphoma complicated by *Aspergillus* pneumonia. At autopsy, *Nocardia* was identified in the regressed abscess cavity of the mesencephalon, but not elsewhere.

III. Ophthalmic Case Reports

A. INCLUSION CRITERIA

Thirty-eight previously published cases with endogenous intraocular *Nocardia* were identified using the methods described in Section VII (Method of Literature Search). Most cases were published in English, with two in German,[96,121] and one in Portuguese.[100] Thirty-seven reports presented clinical data, 17 included histological findings, and one report consisted of ocular pathology[87] with little clinical data. Clinical descriptions were all detailed except one, which was a description of a brain scan.[149] The citation period covers 1967 to 2007. A further report[136] published in 2008 was not included in the clinical analysis. Nevertheless, optical coherence tomography (OCT) descriptions were added. New therapy is discussed in section IV.B.14.

B. EXCLUSION CRITERIA

Case reports where another infection such as tuberculosis could be causing the ocular picture were excluded. One report of hematogenous spread of *Nocardia* to the orbit and a report of external ophthalmoplegia without intraocular involvement were not included. Reports of *Nocardia* of the lacrimal ducts and exogenous *Nocardia* after ocular surgery, trauma, or keratitis are not considered here.

C. METHODS

We analyzed age, sex, underlying diseases, medications, systemic picture of nocardiosis at presentation, its evolution, time to diagnosis, number of ineffective treatments, effective treatments, systemic

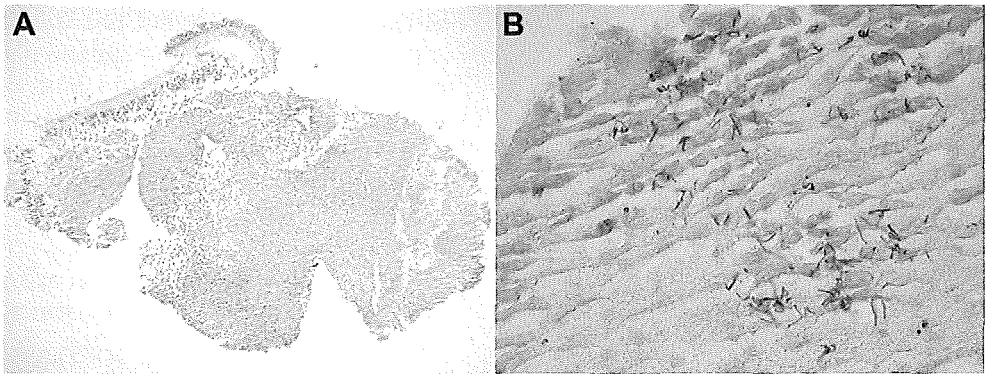

Fig. 2. A: Hematoxylin and eosin staining of a subretinal abscess composed essentially of necrotic tissue infiltrated by polymorphonuclear cells. Note retinal tissue at the top, stemming from the edge of the retinectomy. *B:* Gram stain of the subretinal abscess showing Gram-positive filamentous, branching bacteria characteristic of *Nocardia* species.

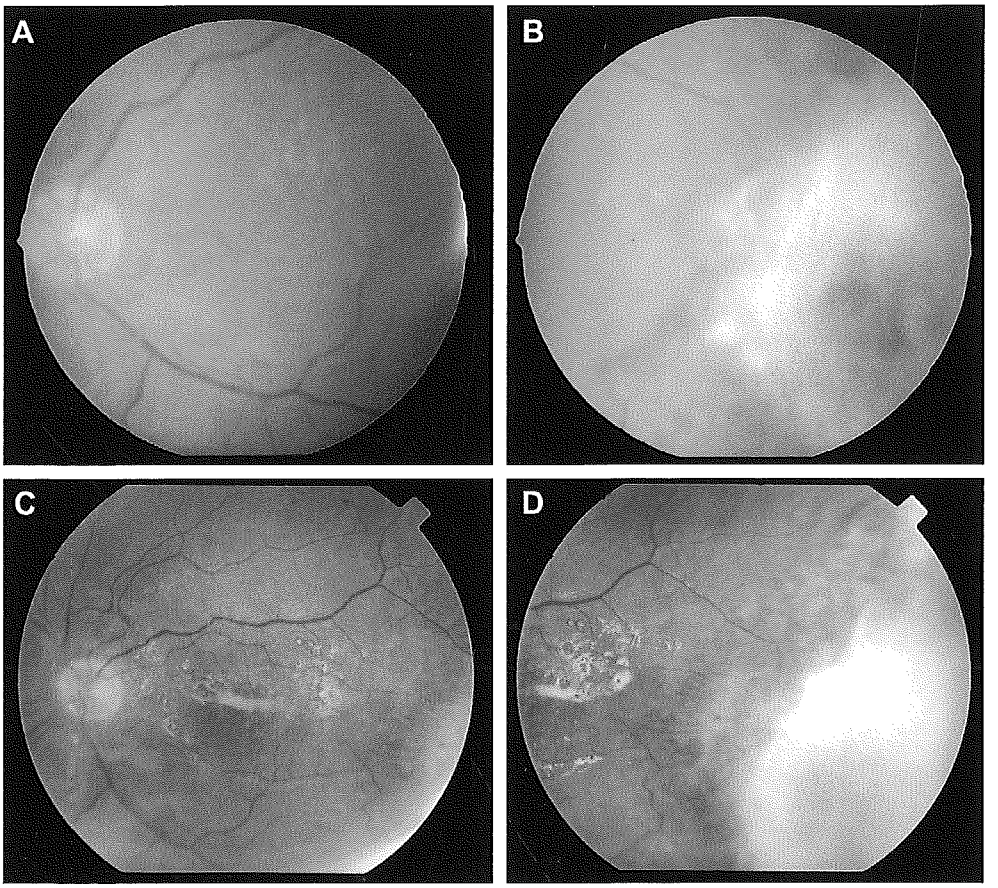

Fig. 3. A and B: Fundus photograph at 1 week after surgery, visual acuity was counting fingers with silicone oil tamponade. The haze is due to corneal edema. Note the area of the retinectomy temporally. *C and D:* Fundus photograph at 3.5 months after surgery showing a completely flat macula under silicone oil tamponade and pigmented laser scars at the edge of the retinectomy. Best corrected visual acuity has increased to 20/25.

recurrences, mortality; temporal relationship of ocular nocardiosis to systemic disease, ocular symptoms, ocular presentation, differential diagnosis, ocular evolution, diagnostic procedures on the eye or elsewhere, complications of ocular diagnostic procedures, outcome of eye after treatment, complications of healed ocular *Nocardia* lesions and its treatment; initial and final visual acuities, enucleation/evisceration, and follow-up time. We considered fluorescein angiographic findings in respect to clinical picture and outcome of treatment and to the location of *Nocardia* identified histologically in treated and untreated eyes. Attention was given to symptoms and signs of severity of ocular disease.

IV. Results of Literature Review of Endogenous Ocular Nocardiosis

A. SYSTEMIC FEATURES AND MORTALITY OF NOCARDIOSIS IN PATIENTS WITH EON

Thirty-seven clinical and one pathologic[87] case were identified and analyzed. Overall, 47 eyes were affected by endogenous intraocular nocardiosis. Table 1 gives an overview of patients' age, sex, *Nocardia* species, underlying disease, steroids, immunosuppressives, and outcome.

1. Species of *Nocardia* Reported in EON

N. asteroides was isolated in 29 (91%) and *N. farcinia* in three (9%) patients. Species was not available in six reports.

2. Age and Sex Distribution of Patients

Patients from 8 to 83 years were affected, with an average age of 47 years and a median of 46 years. Thirty (79%) patients were male, 8 (21%) patients female, a male to female ratio of 4:1.

3. Predisposing Risk Factors

a. Diseases

Almost half (17/37; 46%) of the patients were organ transplant recipients (9 kidney, 5 bone marrow, 3 heart). Nocardiosis occurred within a year

TABLE 1

Study Summaries

Author	Year	Nocardia species	Age	Sex	Underlying Condition	Steroids	Immunosuppressives	Cause of Death
Davidson[33]	1967	NA	46	m	Obstructive jaundice sec. cholelithiasis	0	0	na
Meyer[87]	1970	NA	67	m	Gunshot wound left chest, systemic penicillin, cutaneous ulcer of the wound, pneumonitis not responding to antibiotics	0	0	Sepsis (N)
Meyer[87]	1970	NA	56	m	ns	ns	ns	ns
Burpee[20]	1971	NA	20	m	Booby trap explosion in Vietnam	0	0	na
Panijayanond[99]	1972	NA	50	m	TPK 7–8 months previous for arteriolar nephrosclerosis, duodenal ulcer and surgery, infections	Corticosteroids	Azathioprine, antilymphocytic globulin	na
Jampol[59]	1973	NA	40	m	TPK 3 months ago for Wegener's granulomatosis	Corticosteroids "high dose"	Azathioprine 2–3 mg/kg/day	Sepsis (N)
Sher[123]	1977	NA	38	m	Bruton's sex-linked hypogamma-globulinaemia, various pulmonary infections since infancy, chronic aggressive hepatitis	Prednisone 50 mg/day	0	Sepsis (N)
Rogers[114]	1977	NSPP	77	f	Lymphocytic lymphoma	Prednisone	Cyclophosphamide, Vincristine, radiation	Meningo-encephalitis (N)
Lissner[76]	1978	NA	60	m	Undiagnosed Hodgkin disease, treatment for sarcoidosis, h/o severe pneumonia 30 years ago	Prednisone 60 mg/day	0	Sepsis (N)

(*Continued on next page*)

TABLE 1
Continued

Author	Year	Nocardia species	Age	Sex	Underlying Condition	Steroids	Immunosuppressives	Cause of Death
Bullock[19]	1983	NSPP	15	m	Paroxyxmal nocturnal hemoglobinuria, TPBM 1.5 years ago, GVHD, obstructive jaundice proven drug cholestasis phenomenon on biopsy	Prednisone 60 mg/day	Methotrexate, antilymphocytic globulins	na
Ferry[45]	1988	NA	66	m	Endarterectomy 6 weeks before onset of ocular symptoms	0	0	na
Ferry[45]	1988	NA	49	f	Systemic sclerosis with diffuse interstitial pulmonary fibrosis	Prednisone 60 mg/day	0	na
Mamalis[78]	1988	NA	44	m	TPH 14 weeks previous	Prednisone 30 mg/day	Cyclosporin 340 mg/day, Azathioprine 100 mg/day	na
Price[106]	1989	NA	53	m	0, Fever, cough and weight loss with beginning of disease	0	0	na
Gregor[52]/Knouse[70]	1989	NA	46	m	TPH 3–4 months ago, rejection treated by muromonab-CD3, corticosteroids, DM	Prednisone 20 mg/day	Cyclosporin 1000 mg/day, Azathioprine 100 mg/day	na
Ishibashi[57]	1990	NA	27	m	Systemic lupus erythematosus since age 14, nephrotic syndrome 2.5 months previous	Prednisone 60 mg/day	0	na
Phillips[101]	1992	NA	63	m	Chronic lymphocytic leukemia, h/o several pneumonia	Prednisone	Fludarabine	na
Niehues[96]	1996	NA	62	m	TPK for terminal glomerulonephritis, 3 years of dialysis, 6 months after transplantation, two episodes of acute rejections	Methylprednisolone 500 mg/day for acute rejection 5 days	Cyclosporin 200 mg/day	Status epilepticus secondary Nocardiosis

Jolly[62]	1996	NA	40	f	TPK 5 months ago	ns	Immunosuppressive x	Necrotizing granulomatous meningo-cerebromyelitis with ARDS (N)
Davitt[34]	1998	NA	80	f	H/o recurrent pneumonia, DM, spinal cord ependymoma, cholecystitis, cholecystectomy	0	0	Sepsis
Chaudhry[24]	1998	NSPP	44	m	TPH 8 months previous, idopathic dilated cardiomyopathy	Prednisone	Cyclophosphamide	na
Yap[144]	1998	NA	49	f	Systemic lupus erythematosus, complicated by arterial hypertension, nephritis, psychosis	Steroids	intermittent Cyclophosphamide the past 6 years	na
Suppiah[127]	1999	NA	45	m	TPK 6 months previous for severe hypertension, rejections	Prednisolone 30 mg/day and 500 mg pulsed over 3 days	Cyclosporin 275 mg/day, Azathioprine for 6 months, discontinued about 1 month previously, because 0 white blood cells	na
Tan[128]	2000	NSPP	37	m	TPK 3 months ago idiopathic kidney failure, hepatitis C	Prednisolone	FK 506	na
Lakosha[74]	2000	NF	41	m	TPBM 13 months ago for CML, acute & chronic GVHD, DM	Prednisone	Tacrolismus	Aspergillus pneumonia
Schriever[121]	2001	NF	40	m	TPK 10 weeks ago for polycystic nephropathy, nephrectomy of the diseased kidney 1 week ago	Corticosteroids	Cyclosporin, Azathioprine	na
Korkmaz[71]	2001	NA	29	m	Adamantiades-Behçet disease	Fluocortolen 10 mg/day	Azathioprine 150 mg/day	na
Ng[95]	2002	NA	69	m	Renal failure secondary glomerulonephritis	Prednisone	0	na

(*Continued on next page*)

TABLE 1
Continued

Author	Year	Nocardia species	Age	Sex	Underlying Condition	Steroids	Immunosuppressives	Cause of Death
Azap[9]/ Bozbeyoglu[15]	2002	NA	46	f	TPK 16 years ago, rejection	Prednisolone	Cyclosporin, Tacrolismus	na
Kim[69]	2004	NA	8	m	TPBM 18months for ALL, GVHD	ns	Immunosuppressive x	Recurrence ALL
Moshfeghi[93]	2004	NSPP	19	m	TPBM 15months for AML, GVHD affecting skin, liver, intestines	0	Cyclophosphamide, Daunorubicin, Etoposide, 6–thioguanine	na
Pelayes[100]	2004	NA	32	m	Systemic lupus erythematosus	Methylprednisolone 60 mg/day	Cyclophosphamide 1 g/month	na
Yu[148]	2005	NA	41	f	TPBM 7 months before for leukemia	Prednisone	Cyclosporin	ARDS; Sepsis (N), general seizure
Rafiei[109]	2006	NA	62	m	Idiopathic thrombocytopenic purpura	Steroids	0	na
Heron[54]	2006	NA	83	m	Giant cell arteritis	Prednisone 25 mg/day	0	Sepsis (N)
Dodds[37]	2006	NF	26	f	Systemic lupus erythematosus, chronic renal failure	Prednisone	Cyclophosphamide	na
De Silva[35]	2006	NSPP	49	m	Hepatits C, previously intravenous drug abuser, HIV negative	0	0	na
Zaatreh[149]	2006	NA	55	m	TPK 5 years ago	Prednisone 10 mg/day	Tacrolismus 10 mg/day	na

0 = none; ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; ARDS = acute respiratory distress syndrome; CML = chronic myeloid leukemia; f = female; GVHD = graft versus host disease; h/o =history of; m = male; N = *Nocardia*; NA = *Nocardia asteroides*; na = not applicable; NF = *Nocardia farcinica*; ns = not stated; NSPP = *Nocardia* not specified; TPH = heart transplant; TPBM = bone marrow transplant; TPK = kidney transplant.

from transplantation in 7/9 kidney,[59,62,96,99,121,127,128] 3/3 heart,[24,52,70,78] and 1/5 bone marrow recipients.[148] After 1 year, *Nocardia* affected 4/5 bone marrow recipients[19,69,74,93] (all with graft-versus-host disease) and two kidney recipients, one 16 years after transplantation with a previous episode of acute rejection[9,15] and one after 5 years after transplantation without described previous rejection in a brief report.[149] Nine (24%) patients had an autoimmune disease—systemic lupus erythematosus (4), Wegener granulomatosis (1), glomerulonephritis (1), systemic sclerosis (1), Adamantiades-Behçet disease (1), giant cell arteritis (1). Seven (19%) patients had known hematological malignancy (Hodgkin lymphoma, lymphocytic lymphoma, acute and chronic lymphoid leukemia, acute and chronic myeloid leukemia, one not specified). Four of those underwent bone marrow transplantation. Seven (19%) patients had liver disease—hepatitis or cholestasis of diverse causes (cholelithiasis, cholecystitis, drug induced). In three patients[33–35] this was the major health issue. Two were not treated with antibiotics against *Nocardia* and recovered;[35] one recovered after cholecystectomy.[33] Five (13%) had a recent history of surgery or trauma of an organ other than the eye: one carotid endarterectomy, one surgery for a duodenal ulcer after transplantation, one nephrectomy of diseased kidney after transplantation (transplant surgeries were not counted in this group); traumas were a gunshot in the thorax and a booby trap explosion. One patient had idiopathic thrombocytopenic purpura, one hypogammaglobulinemia, and a child had paroxysmal nocturnal hemoglobulinuria treated by bone marrow transplantation. One had no known underlying disease.[106] Twenty-six (70%) had one predisposing disease, six (16%) had two, two had three, and one had four predisposing diseases. Only three patients had additional diabetes mellitus.[34,52,74]

b. Medications

Thirty-five reports specified the immunosuppressive therapy when *Nocardia* became manifest; two only stated "on immunosuppressives."[69,95] Figure 4 illustrates the different regimens patients were on at presentation. The majority of patients were on steroids (73%), either alone (19%) or in combination with one (35%) or two (19%) other immunosuppressive drugs. Seven patients (19%) had no immunomodulatory therapy (group of trauma, surgery, liver disease, and healthy). Only one patient was on a combination of immunosuppressives (cyclophosphamide, daunorubicin, etoposide, 6-thioguanine) without corticosteroids.[93]

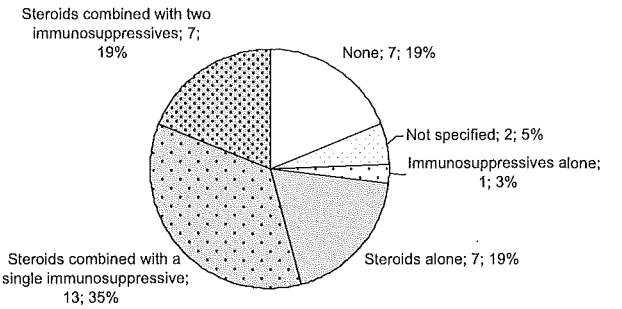

Fig. 4. Frequency of immunocompromizing treatments as reported in patients with endogenous ocular *Nocardia* infection. Steroids were used in over 70% of patients as part of the treatment regimens. A combination of immunosuppressives (4) was reported the least frequently; no report with two immunosuppressives without steroids.

Eleven reports specified prednisone or equivalent dosages ranging from 10–75 mg/day, (mean, 44 mg/day; median, 50 mg/day). Immunomodulatory agents were of the following classes: anti-metabolites (9 times) (azathioprine [6], methotrexate [1], fludarabine [1], 6-thioguanine [1]), T-cell inhibitors (8) (cyclosporin [4], tacrolismus [3], FK 506 [1]), alkylating agent (5) (cyclophosphamide [5]), and diverse (antilymphocytic globulins [1], mitotic inhibitor [vincristine] [1], cytotoxic antibiotic [daunorubicin] [1], and topoisomerase inhibitor [etoposide] [1]). There were only few data about leucocytes and no report of CD4+ T-lymphocytes levels.

4. Systemic Involvement in the Presence of EON

About half of the reports indicated a duration of symptoms that varied from 2 days to 16 weeks, with an average of 3 and a median of 1.5 weeks before presentation. Forty-three percent (43%) of the patients presented with fever and a quarter (24%) with significant weight loss. The lung was affected in 57% at presentation and in 70% during the course of the disease. Dissemination to the brain was diagnosed at presentation in 10 (22%) cases and in a further 9 patients later. Two patients were asymptomatic,[34,101] but had positive brain scans. In all, 51% of the patients had cerebral complications.

Eight (22%) patients had a cutaneous or subcutaneous abscess at presentation, and 11 (30%) patients developed this. Other organs affected were blood (4), joint (3), kidney (2), endocard (1), thyroid (1), spleen (1), liver (1), prostate (1), testicle (1), and penis (1). One patient had a double infection with *Trichophyton rubrum* in his groin.[9,15] Continous dissemination after initial presentation occurred in 23 (62%) patients.

5. Disease Recurrence and Mortality of Patients with EON

In 36 reports the range of follow-up was between 3 weeks (patient's death) and 104 weeks, with a mean of 34 and a median of 26 weeks. Overall, eight (22%) patients suffered from recurrences: five had one,[20,37,59,74,123] two had two,[34,99] and one had three.[127] Twenty-five patients (68%) survived nocardiosis and/or the underlying disease. Ten (27%) patients died from their *Nocardia*.[34,54,59,62,76,87,96,114,123,144] One patient had sulfonamide-intolerance requiring a change in antibiotics that was fatal.[59] Bilateral EON did not confer a bad vital prognosis: seven of nine patients survived. One patient (3%) died due to progression of blood malignancy[69] and one due to pulmonary aspergillosis.[74]

B. OPHTHALMIC FEATURES AND OCULAR MORBIDITY OF EON

1. Laterality of Eye Involvement

Twenty-nine (76%) had unilateral (12 OD, 17 OS) and nine had bilateral eye disease.

2. Temporal Relationship of Ocular and Systemic Symptoms

About half (20 patients, 53%) first sought medical attention because of ocular symptoms. In 10 patients[9,15,37,54,69,74,76,87,121,127,148] EON clearly preceded systemic disease. In seven patients[33,34,62,71,95,99,149] ocular symptoms were associated with various systemic manifestations, and in three patients EON was isolated without any sign of systemic nocardiosis (after endarterectomy,[5] with hepatitis C,[35] and with systemic sclerosis[45]). In the other 18 patients (47%), EON appeared during the course[19,20,52,57,59,70,78,87,96,100,101,114,144] of systemic nocardiosis. Of those, six patients[24,93,106,109,123,128] presented with ocular lesions while being treated with systemic therapy.

3. Ocular Symptoms

Twenty-one reports specified the duration of ocular symptoms that varied from 2 days to 9 weeks (average, 2 weeks; median, 1 week). Taken from 34 reports, 27 (79%) patients complained of reduced, blurred, or cloudy vision. More than one-third of patients (41%) had pain (10) or ocular discomfort (4). A minority had a history of redness (15%), floaters or a scotoma (11%), photophobia (3%), metamorphopsia (3%), or a "white pupil" (3%), which corresponded to a hypopyon. One eye of a patient who had bilateral disease was asymptomatic.

4. Visual Acuity at Presentation

Visual acuity at presentation was reported for 35 out of 47 eyes. Eighteen eyes (51%) had visual acuity equal or worse than 20/200. Two eyes were NLP—one with advanced abscess formation,[114] the second with optic neuropathy and retinal detachment.[45] Fourteen (40%) eyes had VA equal or better than 20/40, three eyes had less than 20/40, but better than 20/200. One patient had a history of posterior uveitis as part of Adamantiades-Behçet disease[71] with visual acuity of light perception. His visual acuity before nocardiosis was not reported.

5. Ocular Findings

Forty-six eyes were described clinically, and one eye was described as endophthalmitis with subretinal abscess without other details.[149]

a. Conjunctiva, cornea, sclera, orbit, exteriorization/perforation

Conjunctival injection was seen at presentation in 11 eyes (24%) and in a total of 15 patients (33%) in the course of disease. Keratitis was not described, only corneal edema in an eye that had perforated[100]and one with angle-closure glaucoma.[34] One of the patients suffered from scleritis,[144] probably at the external side of a subretinal abscess. Proptosis was not a presenting sign, but four[35,74,87,148] eyes (9%) developed it during the course of the disease. In three eyes proptosis was followed by exteriorization.[35,87,148] Two[71,100] additional eyes had exteriorization without mentioned proptosis but both with purulent discharges. In all, in five eyes (10%) the abscess exteriorized. Table 2 gives an overview about the combination of ocular pain, proptosis and hypopyon in these eyes. *N. asteroides* was found in four eyes and *N. farcinia* in one eye.

b. Anterior chamber, iris

In 17 eyes (37%) anterior chamber inflammation was noted. In four eyes there was a hypopyon (9%).[34,100,128,148] Three of those eyes, including the

TABLE 2

Critical Signs for Exteriorization/Perforation of the eyes During EON

Author	Pain	Proptosis	Hypopyon
Meyer[87]	ns	+	ns
De Silva[35]	+	+	−
Yu[148]	+	+	+
Korkmaz[71]	+	−	+
Pelayes[100]	+	−	+

− = absent; + = present; ns = not stated.

patient with Adamantiades-Behçet disease, had exteriorization. One recurrent hypopyon was the only ocular manifestation of nocardiosis.[34] Posterior synechiae[20,109] were found in two eyes at presentation, and one iris granuloma[121] evolved.

c. Vitreous

Fourteen eyes (30%) showed some degree of vitreous infiltration[24,62,95] at presentation, 11 with concomitant anterior chamber reaction.[20,45,57,71,78,109,114,123,144,148] Four of those eyes had severe vitritis.[20,62,114,148] Three more eyes[20,33,99] developed vitritis during the course of disease—a total of 37%.

d. Chorioretinitis, subretinal abscesses

In 35 eyes, the description of the fundus allowed us to gauge the number of lesions per eye. For the other eyes, there was either no view as the result of severe vitritis, a retinal detachment, or the hypopyon was isolated. In some reports the fundus was not described in detail because the authors were not ophthalmologists.

Two-thirds (24 eyes, 69%) had one single lesion described as a mass, an inflammatory mass, or chorioretinal exudate. Superficial or intraretinal hemorrhages were often associated. Eight eyes (23%) had three or more lesions. Three eyes (9%) had two lesions per eye.

The macular region was affected in 24 (69%) eyes,[9,15,20,24,33,45,52,54,57,59,70,74,78,87,99,121] including 7 (20%) eyes with foveolar involvement.[19,45,69,93,95,101,106] The region outside the macula was affected in 12 (34%) eyes,[20,24,37,45,62,76,87,93,123] and the region close to the optic nerve in 5 (14%) eyes.[45,87,106,109,121]

During the clinical course, there was an enlargement of the original lesion in nine eyes (38%).[9,15,57,74,78,87,101,121,123] In two patients[87,123] lesions developed in the fellow, initially unaffected eye. One eye of a heart transplant patient presented with cytomegalovirus (CMV) retinitis shortly after the disappearance of *Nocardia* chorioretinal infiltrates.[24]

e. Serous retinal detachment

Upon presentation, serous retinal detachment was either slight (8) or massive (3) in 1 (31%) out of 35 eyes. One eye's slight retinal detachment increased.[33] Three other eyes developed de novo retinal detachment, one slight[93] and two totally.[45,121] In all, 14 eyes (40%) had retinal detachments. One retinal detachment (funnel shaped) was complicated by secondary neovascular glaucoma.[121]

6. Fluorescein and Indocyanine Green Angiography of Acute and Healed Lesions

Five authors[54,76,78,93,101] reported EON-associated lesions on fluorescein angiography (FA). The earliest three reports looked at acute lesions (Table 3) and the later two at complications after recovery from EON. Phillips[85] and Lissner[76] observed early blockage of choroidal background staining, which confirms the findings documented by Bozbeyoglu[15] using indocyanine-green angiography (ICG), with consecutive hypofluorescence at the lesion in late frames. The middle phase of FA is marked by leakage from the retinal vessels at the margin of the abscess and with their occlusion on the mass.

Of most interest are the late phases of the FA. Mamalis, whose patient responded to systemic treatment, showed accumulation of dye in the subretinal space without diffusion into the

TABLE 3

Comparison of Fluorescein Angiography Findings in Three Reports

Author	Early Phase	Middle Phase	Late Phase	Outcome
Mamalis[78]	Not stated	Leakage of retinal vessels covering the mass	Accumulation of dye in subretinal space	Response to systemic treatment, scar
Phillips[101]	Blockage of choroidal background staining	Diffuse leakage of retinal vessel	Progressive leakage from the lesion	Survived, no ocular response to systemic treatment
Lissner[76]	Blockage of choroidal filling	Leakage at the margins of retinal vessels, occlusion over the mass	Leakage of fluoresceine into the vitreous	Patient died

Note that the eye of the patient of Mamalis responded to systemic treatment. There was no dye diffusion into the vitreous, as the outer blood–retinal barrier remained intact, whereas in the eye of Philips' patient fluorescein leaked in the late phase into the vitreal cavity. In this case there was no response to systemic treatment. Lissner's patient did not receive systemic treatment as *Nocardia* was diagnosed at autopsy. A break of the outer ocular barrier was found in histology.

vitreous.[66] This is in contrast to the report by Phillips, where progressive leakage from the lesion into the vitreous was observed. This eye did not respond to systemic treatment. The same FA observation as in Phillips's patient was found in the eye of Lissner's patient, who died shortly after the FA. Ocular pathology found that

> a suppurative inflammatory process replaced the choroid and extended into the subretinal pigment epithelial space through gaps in the pigment epithelium to involve most of the overlying retina . . . the necrosis was especially intense adjacent to Bruch's Membrane, where the choriocapillaris was totally obliterated. . . . Bruch's membrane appeared intact, but the area between Bruch's membrane and the disintegrating retinal pigment epithelium was filled with amorphous material. The overlying retina was necrotic but the internal limiting membrane was intact [page 390].[76]

This histological observation documents the disruption of the outer blood–retina barrier and with that the potential invasion of the vitreous cavity. It is only a matter of time until the vitreous is invaded if progression of disease cannot be stopped.

The report of Moshfeghi[77] documented the development of a subretinal neovascular membrane fed by a chorioretinal anastomosis 20 weeks after a subretinal abscess had healed. Rafiei[92] documented a fibrovascular scar with tractional retinal detachment. FA showed areas of capillary nonperfusion with secondary retinal neovascularization.

7. Optical Coherence Tomography

Vossmerbaeumer et al[136] had a patient with a subretinal abscess with a serous retinal detachment. FA showed late hyperfluorescence without leakage from the mass, ICG showed blocking. OCT images (Stratus OCT III) documented an "intact sensorineural retina over an adherent, homogenously hyper-reflective nocardioma with massive subretinal fluid [page 382]." The lesion was stable under systemic treatment in contrast to concomitant brain abscesses.

8. Ultrasound Findings of Acute Lesions

Three authors reported the outcome of ultrasound exams of acute lesions: Yap et al reported on a patient who showed a 5–6 disk diameter large yellow flat choroidal lesion that appeared homogenous of low-to-medium internal reflectivity on ultrasound.[117] Lakosha's case showed a kidney-shaped (8 × 6 mm) lesion on ophthalmoscopy with a fluid level (posterior hypopyon) at its inferior aspect and multiple hemorrhages in the overlying retina. On B-scan, there was an irregular elevation with a maximum thickness of 1.7 mm.[61] The superior region showed high reflectivity whereas the inferior aspect was of low reflectivity. A-scan confirmed the fluid nature of the inferior part, and it documented an area of increased reflectivity of the sclera (scleral inflammation) behind the lesion. Bozbeyoglu's patient showed a well-demarcated, white-yellow, elevated choroidal lesion with intra- and subretinal hemorrhages above it.[15] On ultrasound, the mass appeared acoustically hollow and it had a thickness of 2.5 mm.

9. Magnetic Resonance Imaging

Yu et al[148] correlated MRI images of an eye with the histopathological findings after enucleation. Pathologically there was panophthalmitis with infiltration of the sclera, choroid, exudative retinal detachment, and vitreous hemorrhage. T1- and T2-weighted images were helpful in demonstrating scleral thickening, choroidal edema, retinal detachment, and an opaque vitreous. Diffusion-weighted axial images nicely demonstrated a sausage-like lesion in the subretinal space that corresponded to the macroscopic form of the same abscess on a section of the eye.

10. Differential Diagnosis Evoked by the Authors

In 20 reports, the evoked differential diagnoses were, in decreasing order: fungus (7 patients), metastasis (4), toxoplasmosis (4) and underlying disease [Adamantiades-Behçet disease, giant cell arteritis, leukemia, lymphoma] (4), tuberculosis (2), CMV (2), and amelanotic melanoma (1).

11. Time to Diagnosis and Diagnostic Procedures

In 38 reports the time to diagnosis was between half a week and 14 weeks, with a mean of 3.5 weeks. Bullock and Dodds alone made a clinical diagnosis of nocardiosis based on the eye lesions, patients' profiles, and systemic features that was subsequently confirmed by microbiology. In the other reports, the diagnosis was established only on microbiologic findings. In 19 (50%) patients the diagnosis were based on ocular specimens,[33–35,37,45,52,57,70,87,101,127,149] in 7 combined with other sites,[9,15,71,95,100,121,123,148] in 16 (42%) from samples taken elsewhere than the eye,[19,20,24,59,62,69,74,78,87,93,96,99,106,109,128,144] and in 3 (8%) only at autopsy.[54,76,114]

a. Specimens taken from elsewhere than the eye

Specimen were taken from the lung (12) by broncheoalveolar lavage, fine-needle or open lung

biopsies, and one sputum; from skin abscesses (10 biopsies); by blood cultures (4); and one each from the brain, a submandibular mass, and the epidymis (orchiectomy[78]).

b. Ocular specimens taken, successful versus unsuccessful procedures in identifying the pathogen

Diagnosis was established in the published cases after evisceration in one patient,[87] and after diagnostic enucleation in six patients.[33,45,121,127,148] Five vitreal and one anterior chamber taps were performed: all were negative.[34,35,37,95,128] A repeated anterior chamber tap[34] in the patient who had a hypopyon as the only ocular sign of EON was positive on smears and cultures. In three patients PPV was performed. Of those, two revealed *Nocardia* (1 smears and culture; 1 smears alone) [57,100] and one was negative.[148]

Transvitreal subretinal fine-needle aspiration biopsy, as described by Augsburger,[7,52,70] was positive in all four patients on whom it was performed.[9,15,35,101] Two patients[52,70,101] had positive staining and growth in culture, one had prolonged negative cultures and a staining pattern compatible with *Nocardia.*[35] The fourth had positive staining for *N. asteroides,* confirmed by growth of blood cultures.[9,15] PPV combined with aspiration of the abscess was first performed in EON by Sher[123] in 1977, and smears and cultures were positive. Two other reports followed, both with positive cultures (one from the vitreous cavity).[37,95] Overall, from 18 diagnostic samples (enucleations/evisceration excluded), 6 (33%) specimens were negative in smears and culture. Of those samples, five were collected by vitreal taps and one by a PPV (without subretinal biopsy).[148] Either smears and/or cultures were positive in all four patients who had undergone transvitreal fine-needle biopsies, in all PPVs combined with subretinal aspiration biopsy (3), and two of three PPVs without aspiration biopsy of the lesion. *Nocardia* was also found on repeated anterior chamber tap (1), "drainage of subretinal abscess"[149] and collection of "leaking pus" of an eye with exteriorization.[71]

c. Complications related to ocular diagnostic procedures

Four (22%) eyes developed complications: four cataracts (vitreal tap,[128] and vitrectomy alone[57]), two combined with a retinal detachment (transvitreal fine-needle biopsy,[9,15] vitrectomy combined with aspiration of subretinal abscess[95]).

12. Number of Ineffective Treatments before Diagnosis

From 36 reports, 17 patients benefited from adequate treatment from the start; 11 patients had one and 8 patients had two to four ineffective treatments before the definitive therapy was instituted.

13. Efficacy of Trimethoprim-Sulphamethoxazole

TM-SMX was an effective systemic treatment in 8 (22%) patients;[20,52,67,70,71,74,123,127,149] in 6 patients it was given in combination with other antibiotics.[9,15,93,95,100,101,109] TM-SMX was not effective in five (13%) patients.[37,57,62,106,128] Cephalosporines, amikacin, imipenem, ciproxine, and sulphonamide were used alone or in various combinations.

14. Responses of Eyes Exposed to Effective Systemic Antibiotic Treatment and Eyes that Failed to Respond

Effective systemic antibiotic treatment was defined as a systemic antibiotic that *Nocardia* is known to be sensitive to and a clinical response elsewhere—for example, regression of brain abscess documented on MRI. Twenty-seven eyes (57 %) benefited from such a treatment. Of those, 20 eyes (74%) had a favorable response.[9,15,19,20,24,52,57,69,70,74,78,93,95,106,109,123,128,144] Five eyes,[20,71,99,100,101] all infected with *N. asteroides,* did not respond; in two eyes, the outcome was uncertain at the end of follow-up.[37,128] The principal cause of failure was very advanced infection: one bilateral case[20] had response of early lesions in one eye, but not of advanced lesions in the other eye under systemic sulfadiazine and chloramphenicol. A unilateral case[99] was treated late in the evolution of disease with sulfisoxazole 4–6 g/day, but after 11 days of treatment the eye was considered lost. A third patient[101] was treated by intravenous (IV) TM-SMX, but there was enlargement of the lesion over the course of disease with simultaneous regression of brain lesions. After repeated intravitreal injections of 400 μg amikacin and 2.25 mg cephazolin over 3 months, the lesion transformed into a scar. One patient[71]with Adamantiades-Behçet disease was treated for pneumonia with ceftazidine and clarithromycin until development of severe orbital pain. Thereafter, he received ceftriaxone and ciprofloxacin for presumed endogenous endophthalmitis. After scleral perforation, the diagnosis of EON was established and he received TM-SMX. The eye was not enucleated but vision was completely lost. The last[100] of the five patients had exteriorization of the disease at presentation and was treated by amikacin, meropenem, then TM-SMX and imipenem. Additional intravitreal injections of 200 μg amikacin and 1mg vancomycin did not salvage the eye. Four of the five eyes had such advanced intraocular infection that systemic treatment was not therapeutic.

15. Systemic Recurrences by Sequestered *Nocardia* in the Eye

In Burpee's patient both eyes were affected.[20] The eye with the older lesion did not heal under systemic treatment. Indeed, the patient suffered from repeated systemic recurrences without identification of a persistent systemic focus. Recurrences subsided after enucleation. This case illustrates that *Nocardia* may sequester in the vitreous and be the cause of systemic recurrences and death unless the eye is treated.

16. Evolution of Lesions after Initial Treatment, Secondary Complications, and their Treatment

For 14 eyes, further evolution was reported. In eight eyes the abscess transformed into a chorioretinal scar.[19,20,24,52,70,74,78,101,144] Early lesions having "multiple small exudates regressed to form punched out chorioretinal scars surrounded by light pigmentation resembling scars of presumed ocular histoplasmosis [page 669]."[20] Two eyes developed subretinal neovascularization with hemorrhage, one[19] after about 36 weeks and a second[93] after 20 weeks. The former patient had a chorioretinal scar measuring two disk diameters below the optic nerve with fingerlike projections to the fovea. Visual acuity was initially 20/30 in the acute phase of the abscess, dropped to 20/100, and stabilized after 2 years at 20/60. The second eye had a parafoveal abscess that transformed into a macula pucker with a secondary subfoveal choroidal neovascular membrane fed by a chorioretinal anastomosis. The anastomosis was preoperatively photocoagulated, and the subretinal membrane excised, leaving a juxtafoveal area of atrophic retinal pigment epithelium and a parafoveal chorioretinal scar. After 8 months of follow-up, visual acuity was 20/20.

A further patient initially showed a large subretinal abscess with overlying retinal perivascular sheathing that transformed into an extensive fibrovascular scar after three months[109] associated with a tractional retinal detachment and cataract. A cataract also developed in another eye with retinal detachment after fine-needle aspiration biopsy[9,15] and in a third eye[57] where the posterior segment was not described further. One eye had persistent macular edema after cataract extraction.[128] Two patients developed secondary glaucoma.[34,109] One eye ended in phthisis bulbi[95] requiring enucleation.

17. Significance of Ocular Pain during EON

Ten patients complained of pain at initial presentation. Three patients[9,15,52,70,123] benefited from quick diagnosis and systemic treatment with disappearance of pain. One eye was already perforated.[100] The eye of three other patients[35,71,148] perforated thereafter (two retained the globe, one demonstated scleral perforation on pathology). Two of these patients had proptosis prior to the perforation. Two other painful eyes were enucleated, one because of a completely "destroyed" eye[99](scarce pathology) and one to obtain a diagnosis.[45,99] Histological examination of the latter demonstrated next to the subretinal abscesses a moderate inflammation of the iris and an unremarkable sclera. One patient's ocular pain was probably due to anterior chamber inflammation.[109]

Four patients complained of ocular discomfort: One patient suffered during the evolution of the disease from frank pain with proptosis that improved with systemic treatment and recurred after withdrawal of treatment.[74] An ultrasound examination demonstrated increased reflectivity behind the abscess in the sclera. The second patient received 10% sulfacetamide drops before ophthalmologic examination that considerably improved his discomfort despite a subretinal abscess in the back of his eye.[76] Pathology showed no anterior segment inflammation and infiltration of the vitreous body adjacent to the abscess. The third patient had a painful, blind eye that was enucleated because of systemic recurrences thought to be metastatic from the eye.[20] Pathologic findings demonstrated infiltration of the iris with chronic inflammatory cells, fibrin between the two leaves of the iris, the absence of scleral inflammation and sequestration of *Nocardia* in the vitreous. The last patient had an isolated hypopyon.[34]

During the evolution of disease, two patients complained about new pain: one underwent diagnostic enucleation.[33] The subretinal abscess showed infiltration up to the ciliary body. The other was enucleated for "endophthalmitis"; histopathologic description was not provided.[127]

Of great value is the report of Meyer[87] who described an eye with a history of "fulminant" chorioretinitis: "Shortly, the eye became proptosed, and a mass developed over the lateral aspect of the globe. This mass appeared as though an abscess was forming and exudate was pouring from it [page 538]." Microscopically, there was an intense inflammatory reaction of the sclera and *Nocardia* was identified within the sclera.

Sixty-six percent of 14 painful eyes were reported to have cells (mild to hypopyon [4]) in the anterior chamber. In the 18 other reports not describing pain or ocular discomfort, there were cells in the anterior chamber in 33% (mild to hypopyon [1])[128]. This hypopyon was observed in a patient who lost consciousness shortly thereafter; the patient benefited from subconjunctival amikacin injections as an adjunct to systemic treatment.

There was no exteriorization/perforation or proptosis during evolution in the group without pain. Their pathology[45,59,95,114,121] (5) did not show iris/ciliary body or scleral inflammation. Pain in the eye in the acute phase of EON indicates iridocyclitis (5)[20,33,45,76,109] and/or scleritis with or without concomitant orbital infiltration. Perforation is imminent (3 eyes with proptosis [35,74,148] and 2 without prior proptosis[71,100]).

18. Pathology Findings Reported of Untreated Eyes, of Eyes with Treatment Failure and Eyes that Responded to Systemic Treatment

An overview of the findings of 17 ocular pathology reports is given in Table 4. The specimens for pathology were taken at different time points during the disease: at autopsy (7 eyes), after diagnostic enucleation (5 eyes), after systemic treatment with no ocular response (3 eyes) and after good therapeutic response (2 eyes). One of the eyes that responded to treatment ended in phthisis,[95] the second came from a patient[123] that succumbed after a recurrence of nocardiosis after a change of antibiotics.

In the 12 eyes never exposed to systemic treatment, *Nocardia* was identified in the choroid, Bruch's membrane, subretinal space, and the retina in all 12 eyes and in the vitreous in one eye. This is in contrast to three eyes exposed systemically to appropriate antibiotics and enucleated for treatment failure.[20,99,100] In these eyes *Nocardia* was identified only in the vitreous cavity. At initiation of treatment, these eyes had advanced disease (visual acuity light perception, massive retinal detachment;[20] cloudy subretinal mass and delay of treatment by 2 weeks;[99] eye with exteriorisaton[100]).

Two eyes treated with appropriate antibiotics were enucleated for the reasons mentioned previously. In both, no organisms were identified. Both had a short delay in diagnosis (1–2 weeks) and a subretinal abscess at presentation. It is plausible that the vitreous was not invaded when treatment was initiated.

19. Overall Evolution of Eyes, Visual Acuities of Survivors

The overall outcome of all affected eyes but one[149] is illustrated in Figure 5 (gray points at the y axis are those eyes whose visual acuities at presentation were not described).

Analysis in respect to best or worst eye is documented in Table 5.

Of 37 patients, 12 patients (32%) died (14 eyes; nocardiosis and other reasons). Of the survivors, 10 (31%) eyes had visual acuties equal or better 20/40; one (3%) eye's visual acuity was between 20/40 and 20/200; 11 (34%) eyes had visual acuities equal or less than 20/200. Nine eyes were enucleated and one eviscerated (31%).

V. Discussion

A. COMPARISON OF OPHTHALMIC REPORTS WITH NOCARDIOSIS IN GENERAL

The cases published in the ophthalmic literature are similar (age distribution, strong male predominance, underlying diseases, corticosteroids as major risk factor, clinical picture of fever, weight loss, skin lesions, and mortality) to those from the non-ophthalmic literature.[11,81,119] Underrepresented in the ophthalmic literature are patients with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) (see subsequent discussion) and patients with chronic pulmonary disease.[88] Pulmonary disease complicated by nocardiosis is associated with a high one-week mortality (62%), although only 25% of deaths were attributed to nocardiosis itself. Organ transplantation in our study and others[88] is the most common underlying medical condition, followed by HIV and chronic obstructive pulmonary disease. Autoimmune diseases and hematological malignancy treated with bone marrow transplants were slightly more frequent in EON. Hematological malignancies were twice as frequently associated with nocardiosis as solid tumors.[130] Graft-versus-host-disease was suggested as a risk factor for nocardiosis in two studies,[13,31] whereas one study found no difference.[133] In ophthalmic patients, almost 20% of patients had liver disease. Hepatitis B and C or other hepatic disease was found to be a predisposing factor by at least two authors describing nocardiosis in renal transplants.[72,108] A healthy person figures equally to another review[88] with 3%. Pulmonary infection was present in 70% of patients in other studies of nocardiosis[88] as well as in the reviewed ophthalmic cases. Radiologic findings[88] cited in decreasing order were infiltration (60%), nodules (35%), cavitation (13%), and pleural effusion (13%)—bilateral twice as often as unilateral. Thoracic computed tomography revealed pathology in 12 of 15 patients.

Brain involvement occurs in about half the cases of EON and is more frequent than in other series, such as *Nocardia* in transplant patients, but less when disseminating cases alone are analyzed (20% disseminated, 15% to the brain).[11] Mortality increases with brain involvement and with the number of cerebral abscesses.[79]

B. COMPARISON OF OUR CASE WITH THE OPHTHALMIC REPORTS

Our patient presented many of the typical features of nocardiosis: male sex with hematological

TABLE 4

Pathology Findings of Posterior Segment Descriptions

Circum-stance	Author	Vitreous with Culture Positive	Retina	Subretinal Space	PE	Break of BM	Choroid	Nocardia Found
A	Meyer[87]	ns	destruction of photoreceptor, outer nuclear layer	neutrophils, nuclear debris, free pigment granules	disrupted, detached	1	heavy infiltration of inner choriocapillaris	BM, subretinal space, in the retina
A	Meyer[87]	0	ns	abscess	ns	1	necrosis, abscess, hemorrhage	BM, cornea, sclera, in the retina
A	Jampol[59]	0	RD, necrosis, degeneration	debris	disrupted	0	thickening, infiltration, hemorrhage, abscess	BM, choroid
A	Sher[123] OD	0, condensation strands	necrosis, hemorrhage	ns	detached	1, interrupted	necrosis	BM, choroid, retina, (second eye, antibiotic changed→death)
A	Rogers[114]	1	necrosis	RD, abscess	necrosis	1	1, granuloma with giant cells	Subretinal abscess, retina, choroid, vitreous
A	Lissner[76]	0, some infiltration by mononuclear	infiltrated, necrotic	abscess	disrupted	intact	invasion of choriocapillaris, abscess, necrosis	BM, choroid, subretinal PE space, In necrotic retina, N in the abscess cavity
A	Jolly[62]	0, infiltrated	total RD	granulom. abscess with histiocytes, rare multinucleated giant cells	ns	ns	ns	subretinal abscess, PE
DE	Davidson[33]	brownish, liquefied	destruction	abscess, hemorrhage	ns	1	infiltration	abscess subretinal space

DE	Ferry[45]	0, cloudy, hemorrhage, clumps of cellular material, fibrin, infiltrated	total RD	abscess	disrupted, multiple detachment necrotic	intact, with N on it	infiltration, microabscess inner choriocapillaris	BM, inner choroid, subretinal space
DE	Ferry[45]	0, proteinaceous exudates, mild to moderate infiltration	total RD, necrotic, abscess	abscess	ns	1, focally destroyed	infiltration, choriocapillaris, abscess formation, epitheloid and giant cells	subretinal abscess, PE
DE	Schriever[121]	0	ns	infiltrated	ns	ns	ns	epi-, intra-, subretinal, choroidal
DE	Yu[148]	purulent	RD	abscess	ns	ns	infiltrated	choroid
TF	Burpee[20]	1	RD total	ns	ns	ns	infiltration	vitreous
TF	Panijay-anond[99]	1,large hemorrhagic abscess	necrotizing chorioretinitis	ns	ns	ns	ns	vitreous
TF	Pelayes[100]	ns	ns	ns	ns	ns	fibrosis	necrotic intraocular mass
TS	Sher[123] OS	0, clear, status post PPV	gliosis, degeneration	choroidal necrosis	detached	1, destroyed	fibrosis	negative (treated surgically and systemically)
TS	Ng[95]	0	extensive RD	extensive subretinal proliferation	ns	ns	serosanguinous ciliochoroidal effusion	no organisms found after 6 months systemic treatment

1 = positive finding; 0 = negative finding; A = autopsy; BM = Bruch's membrane; DE = diagnostic enucleation; N = *Nocardia*; ns = not stated; PE = pigment epithelium; RD = retinal detachment; TF = treatment failure; TS = treated successfully.

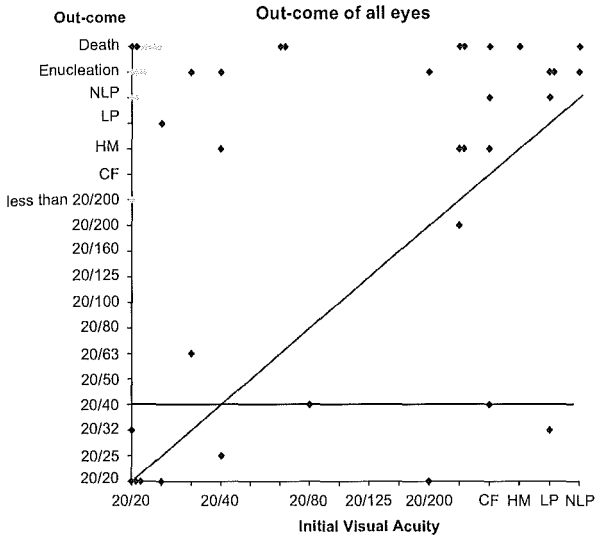

Fig. 5. This chart summarizes the overall outcome and final visual acuities of all eyes. For the gray points on the *y* axis under the terms enucleation and death, initial visual acuity was not documented. From all patients one-third died, one-fourth lost one eye, and less than one-fifth retained visual acuities over 20/40. Or in other words, from the survivor's perspective, about a third of eyes retained good visual acuity of 20/40 or better, about a third had visual acuities 20/200 or less, and about a third of survivors were treated by enucleation.

malignancy treated with high doses of steroids and chemotherapy, and shortly thereafter appearance of a unilateral, single subretinal mass with an initially inconclusive vitreal tap. He subsequently developed encephalitis. Only an invasive vitreoretinal procedure clarified the etiology and allowed adequate systemic antibiotic treatment. The improvement of visual acuity from HM to 20/25 was exceptional.

C. HISTORY AND EPIDEMIOLOGY

Edmond Nocard, a veterinarian, first isolated the pathogen from a bovine farcy (lymphadenitis) in Guadeloupe in 1888.[97] Two years later, Eppinger reported the first human nocardial infection.[40] Since then, a spectrum of disease ranging from benign skin infections to chronic actinomycotic mycetomas (by direct inoculation), and from self-limited bronchopulmonary infections (by inhalation) to severe hematogenous disseminating disease, has been recognized. By means of DNA sequencing, the genus is quickly growing; at least 90 species are identified as of December 2009.[A] Currently, 16–25 species have been implicated in human disease.[17,27,119] The most important are *N. asteroides complex* (*N. asteroides sensu stricto, N. farcinica, N. nova*), *N. brasiliensis, N. otitidiscavarium,* and *N. travelensis.* The taxonomy is in constant evolution.[17] In 1988,[27] only three *Nocardia* species had been identified: *N. asteroides, N. brasiliensis,* and one not stated.[138]

Wallace et al[138] described six drug patterns (I–VI) to which 78 *N. asteroides* isolates were susceptible and suggested that more species are in the same group. Later, drug patterns I, III, and V have been determined to belong to *N. abscessus,*[145] *N. nova,*[131,137] and *N. farcinica,*[139] respectively. *N. asteroides* drug pattern type VI recently has been attributed to the species of *N. cyriacigeorgica* by means of DNA–DNA hybridization.[28] Thus, the group of *N. asteroides* was until recently heterogeneous and because of this in the newer literature is called *N. asteroides complex*; by conclusion, the published cases of EON indicating *N. asteroides* as infectious agent were not necessarily caused by the same species.

Various epidemiological reports are published, but they are difficult to compare due to heterogeneity (single hospitals,[21,81,90,103] several hospitals,[38,43,44] one laboratory,[51] entire countries[49,64,105]). Reported annual cases are listed in Table 6. Clusters of infections during construction work[116,120] or other situations (nosocomial outbreak)[42] are reported. Filice[46] reviewed and calculated the incidence of nocardiosis from articles published between 1966 and 2004. He estimated the incidence of nocardiosis in a general population (USA, Australia, France) to be 0.35–0.4 cases per 10^5 persons/year, a figure recently confirmed by a Spanish study.[88] In the HIV-infected population he estimated 53 cases per 10^5 persons/year, and in bone marrow transplant recipients, 128 cases per 10^5 persons/year. The frequency estimated in a HIV population was 608 cases per 10^5 persons, and in a variety of transplanted organs recipients at 1,122 cases per 10^5 persons.

Infection with HIV is the main risk factor in some clinics.[21,63,103] Some *Nocardia* patients were newly discovered to be HIV-infected. Low CD4+ T-lymphocytes (<100–50 cells/mm^3)[21,102] are

TABLE 5

Final Visual Acuity in Reported Patients

	Best Eye		Worst Eye	
Final Visual Acuity	(No. Patients)	(%)	(No. Patients)	(%)
≥20/40	7	28	5	20
<20/40	1	4	0	0
≤20/200	1	4	1	4
CF	0	0	0	0
HM	4	16	4	16
LP	1	4	1	4
NLP	3	12	4	16
Enucleation	8	32	10	40

CF = counting fingers; HM = hand movement; LP = light perception; NLP = no light perception.

7 patients had bilateral disease.

TABLE 6

Epidemiology Reports of Various Countries/Hospitals

Author	Geography	Study period	*Nocardia spp*	No. Cases/year
Frumkin[49]	Israel	1965–1989	17	0.7
Pintado[102]	Madrid, Spain	1978–2001	34	0.7
Farina[44]	Nine city hospitals, Italy	1982–1992	30	3
Georghiou[51]	One laboratory Queensland, Australia	1983–1988	36	6
Matulionyte[81]	Geneva, Switzerland	1989–2003	20	1.3
Kageyama[64]	Entire Japan	1992–2001	303	33.3
Farina[43]	Eleven cities in Italy	1993–1997	26	5.2
Moiton[90]	Bordeau, France	1993–2003	11	1
Dominguez[38]	Five local hospitals, Texas, USA	1994–1997	12	4
Poonwan[105]	Entire Thailand	1996–2003	96	12
Castro[21]	Miami, Florida, USA	1999–2004	25	4.2

All species of *Nocardia* are included.

associated with nocardiosis in HIV. A study of 10 HIV-positive patients found T lymphocytes at 62 ± 21 cells/mm^3 and a mean viral load of 86,500 copies/mL (median 48,000 copies/mL; range 0–397,000 copies /mL).[88] Only one of those patients was on antiretroviral therapy. The overall incidence of nocardiosis among HIV-infected patients, however, is low in Spain (0.38%),[102] and the United States (0.19–0.3%),[68] but is more common in certain regions of Africa (4%).[63] Highly active antiretroviral therapy is expected to reduce the risk for nocardiosis through the recovery of cell-mediated immunity. Prophylactic TM-SMX to prevent *Pneumocystitis carinii* infection does not seem to be protective against nocardiosis when prescribed three times weekly,[102] but may be more effective when given daily for 6 months post-transplantation[4] or in an HIV-population.[50]

Higher prevalence of nocardiosis in males is typical, except in systemic lupus erythematosus, where in one study 19 of 31 patients (61%) were females.[91] Mortality, however, was higher in males with systemic lupus erythematosus and *Nocardia.*

D. MICROBIOLOGICAL PROPERTIES OF *NOCARDIA*, COLLECTION OF A SPECIMEN, SMEARS AND CULTURES, THEIR SENSITIVITIES AND PCR STUDIES

Nocardia are aerobic actinomycetes that belong to the family of *Nocardiaceae.* As in related high-GC content bacterial families such as *Mycobacteriaceae* and *Corynebacteriaceae* the cell wall of nocardial species contains tuberculosteraric acid.[119] The genus of *Nocardia* encompasses strictly aerobic bacteria. *Nocardia* are bacillary, branching bacteria of 1 μm diameter whose hyphae often fragment to coccobacillary forms. They are Gram-positive, but staining may be only weak and in a irregular manner[14] (sensitivity 65%, see subsequent discussion). They are partially acid-alcohol resistant to modified Ziehl-Neelsen staining and usually stain with modified acid-fast (Kinyoun) stain. In culture, *Nocardia* are slow-cycling. They may take several days to weeks to grow to form white to yellow to orange colonies.

For diagnosis, the presence of the bacteria is the accepted criterion,[14] except in sputum and gastric fluid,[14] because of possible presence of *Nocardia* in food. Multiple specimens must be taken as the bacteria is difficult to visualize because of the low number in tissues. Specimens may be taken by puncture or biopsy from virtually every organ. In the presence of confirmed pulmonary nocardiosis, diagnostic cerebral puncture is contraindicated[14] because of a high risk of meningeal contamination, except in AIDS or severely immunocompromized patients who harbor sometimes more than one organism in one abscess. In the immunocompetent patient with brain abscesses smaller than a diameter of 2 cm, a trial of empiric treatment is thought to be sufficient. For abscesses larger than 2.5 cm diameter, craniotomy for the excision of the abscess has been recommended.[79]

To ensure appropriate staining and culture handling, the suspicion of nocardiosis should be communicated to the microbiology laboratory. Direct stains are of major importance because of the rapidity of diagnosis. Because of emerging resistance, especially for *N. farcinica,* every effort to obtain cultures should be undertaken. Ordinary cultures such as blood agar, chocolate agar, and Sabouraud medium are suitable. Gentamicin in mold agar might inhibit the growth of certain species. If contamination by commensal bacteria

occurs, which might inhibit *Nocardia* growth, a selective medium such as modified Thayer-Martin agar with antibiotics may be used.[119] Cultures are incubated at 32–37C in aerobiosis and eventually with 5–10% of CO_2, which enables more rapid growth. Colonies appear after 2–3 days, but in samples containing very few bacteria, growth may take as long as 2–3 weeks. Twenty (20) days were reported as average time for culture to be processed, and presumptive identification was available after 4–7 days.[12] Twenty percent (20%) of isolates were eventually considered nonsignificant in one microbiological laboratory.[51] Factors important for determination of clinical significance are the direct visualization on Gram staining, pure or predominant growth in culture and repeated isolation of *Nocardia* in serial specimens. Gram is the most sensitive staining technique, with sensitivity estimated at 65%, and that of cultures, at 95%.[119] Modified Kinyoun[14,119] stain is used to confirm the organism detected by Gram staining, which may be unreliable used alone, and distinguishes between *Nocardia* and bacteria *Actinomyces* and *Streptomyces*.

A lot of effort has gone into developing molecular methods for *Nocardia* identification. PCR analysis for clinical specimens such as biopsies, pus, and bronchoalveolar liquid are now available that assist with identification of species by means of sequencing 16S rRNA gene and/or heat shock protein 65 (hsp65).[16,30,113,142] Sequencing of hsp65 was recently used to identify *Nocardia* on the species level in external eye disease and one vitreal specimen.[146] Most sensitive (300 bacteria in 2 μL or 90% sensitivity with negative predictive value at 80% and 100% specificity and positive predictive value) are techniques combining real-time PCR with SYBR Green dye, an intercalating dye attaching to double stranded DNA,[3] available in some laboratories. This technique can be completed in a few hours, compared to about 2 weeks by conventional, phenotypic methods.

Currently, direct staining, culture, and the antibiogram remain the pillars of therapeutic management, as there are variable sensitivities to antibiotics within the group of *Nocardia*. Four smears should be prepared for Gram, acid-fast, modified acid-fast, and fungus. Routine cultures including cultures for tuberculosis should be started. PCR methods enhance diagnosis, but antibiogram remain crucial to guide therapy.

E. RISK FACTORS, STEROIDS, AND IMMUNOSUPPRESSIVES IN ANIMAL MODELS OF EON

Nocardia has a low virulence and only becomes pathogenic when inhaled in high concentration (before 1950, bringing in the hay), in immunocompromized patients, or by direct inoculation during surgery or trauma. Besides pre-existing disease, corticosteroids are the main risk factor (62% in a recent study[88]). These 23 patients received a median dose of steroids of 25 mg (range, 10–80 mg; with transplant recipients and patients with chronic pulmonary disease on the lower end and autoimmune diseases on the higher end) for a median duration of 3 months (range, 1–60 months). Three of 7 organ transplant recipients recently had an acute rejection. In EON, 73% of patients were on steroids. Table 1 enlists the regimens patients were on. Corticosteroids have been shown both to decrease the mean lethal dose for *N. asteroides* sevenfold in mice[89] and to increase the susceptibility for developing subretinal abscesses[19] in rabbits. Figure 4 illustrates the immunosuppressives patients were on at diagnosis of *Nocardia*. The percentages of treatment regimens are parallel to the surprising results found by Bullock in his animal models:[19] Rabbits pretreated with cyclophosphamide alone (here, one immunosuppressive) were less susceptible to ocular infection after inoculation of *Nocardia* in the animal's carotid than those pretreated with saline (here, on no immunosuppressive). The effect of cyclophosphamide found by Bullock was thought to be due to the suppression of B-cells and their influence on T-suppressor cells.[19]

F. DELAY IN DIAGNOSIS, DIFFERENTIAL DIAGNOSIS WITH RESPECT TO MICROBES POSSIBLY INVOLVED

In the absence of clinical suspicion, a delay in diagnosis of up to 4 weeks is common.[81] This delay is clinically important, as there is proliferation of the germ and possible dissemination, which influences the mortality rate.[126] The minimal inhibitory concentration (MIC) increases with a bigger size of the inoculum,[5] making treatment more difficult in more advanced cases.

The etiologic agents, the preferential hematogenous spread to the choroid or retinal vessels, the rapidity of evolution, and the clinical picture may help to distinguish among various endogenous endophthalmitides.

In the differential diagnosis, fungi were the most often mentioned. *Candida*, followed by *Aspergillus*, are the most frequent causes of endogenous fungal endophthalmitis.[125] *Candida* endophthalmitis[86] is easier to exclude as it presents with multiple cotton-wool-like retinal infiltrates and with white string-of-pearl-like agglomerates in the vitreous.[110] In contrast, *Nocardia* appears to have a predilection for

TABLE 7

Calculated Intervals of Intravitreal Amikacin Injections

Eye	Half-life T1/2 (hours)		Intravitreal Concentrations (μg/mL)			Frequency of Injections (days)	
	Rabbit	Human	After Injection	After 4*;T1/2	After 5*;T1/2	4*;T1/2	5*;T1/2
Normal	25.5	43.4	100	6.25	3.125	**7.2**	**9.0**
Aphakic	14.3	24.3	100	6.25	3.125	**4.1**	**5.1**
Aphakic, vitrectomized	7.9	13.4	100	6.25	3.125	**2.2**	**2.8**
Phakic & inflammation	15.5	26.4	100	6.25	3.125	**4.4**	**5.5**
Aphakic & inflammation	7.4	12.6	100	6.25	3.125	**2.1**	**2.6**
Aphakic, vitrecomized & inflammation	7.7	13.09	100	6.25	3.125	**2.2**	**2.7**

Injections as 400 μg/mL in 4mL vitreous as a function of variable clearance of the human eye to maintain vitreal concentrations above MIC for amikacin.

the inner choroid,[19,62,114] forming subretinal abscesses and invading the vitreous late. *Aspergillus* forms subretinal abscesses[147] similar to *Nocardia* but, by its fulminant course, quickly invades the vitreous. Vitreous specimens are often positive for *Aspergillus.*[147] Systemic risk factors for *Aspergillus* are similar to those for *Nocardia.*[110]

Endogenous endophthalmitis with *Pseudallescheria boydii,* an opportunistic fungus[125] (with the asexual forms called *Scedosporium apiospermum*[58] and *Scedosporium prolificans*[132]) affecting immunocompromized patients, was recently described. When affecting the posterior pole, these infections might initially look like EON, but with quicker invasion of the vitreous.[58,132] *Pseudallescheria boydii* characteristically possesses enzymes dissolving the posterior lens capsule.[83] Histologically, *Pseudallescheria boydii* is indistinguishable from *Aspergillus* as its dichotomes hyphae branch at 45°. However, cultures look different, and there is resistance to conventional antifungals[83] with limited sensibilities to voriconazole.

Bacterial causes of subretinal abscesses include *Klebsiella pneumonia,*[53,55,143,147] *Pseudomonas aeruginosa,*[36,140,141] *Staphylococcus aureus,*[26] *Streptcoccus viridans,*[112] and *Streptococcus pyogenes.*[29] *Klebsiella pneumonia* subretinal abscess has a fulminant course, is associated with diabetes mellitus, and produces hepatic abscesses in 50% of the cases.[53] It appears to be more frequent in East Asia. *Pseudomonas aeruginosa* typically colonizes the lungs of patients with bronchiectasis[141] or cystic fibrosis[36] and can recur after lung transplantation.[140]

Clinically, it is surprising that tuberculosis was mentioned only twice as an initial diagnosis. A single tubercle is, after disseminated choroiditis, the second most common clinical presentation of tuberculosis.[118] Indeed, the cell wall composition of *Nocardia* and *Mycobacterium tuberculosis* share a common constituent—tuberculosteraric acid. Furthermore, *Mycobacterium tuberculosis* resembles *Nocardia* in that both are slow-cycling organisms with a relative prolonged clinical history. In contrast, however, tuberculosis is not as ubiquitous, so that infection is not a particular concern, especially in relationship with immune suppression (except for TNF-α blocker).

Nocardia may look like a choroidal tumor/metastasis, by the relative absence of intraocular inflammation. Finally, two patients with known autoimmune diseases (Adamantiades-Behçet Disease and giant cell artertitis) and two with hematological malignancies (leukemia and lymphoma) were thought to have recurrences of their initial disease.

G. ROLE OF FLUORESCEIN ANGIOGRAPHY IN THE DIAGNOSIS AND TREATMENT, TRANSVITREAL SUBRETINAL FINE-NEEDLE BIOPSY VERSUS PARS PLANA VITRECTOMY

Figure 6A illustrates an algorithm of how to manage a patient suspicious for EON. Transvitreal subretinal fine-needle aspiration biopsy, as described by Augsburger[6,7] was successful in yielding the diagnosis of nocardial subretinal abscess in all cases in where it was used.[9,52,101] It should be considered when the pigment epithelium appears intact—that is, when the fluorescein angiogram shows an early choroidal filling defect without late leakage from the mass into the vitreous. The technique of fine-needle aspiration consists of puncturing the subretinal abscess transvitreally via the pars plana using a 22–30-gauge sharp disposable hollow-lumen needle, which is slightly bent at the tip. The length of the needle depends on the location of the mass. The needle is connected via standard plastic tubing to a 10-mL aspiration syringe for the collection of the specimen. The technique is safe in trained hands. Major risk factors are retinal detachment and cataract.

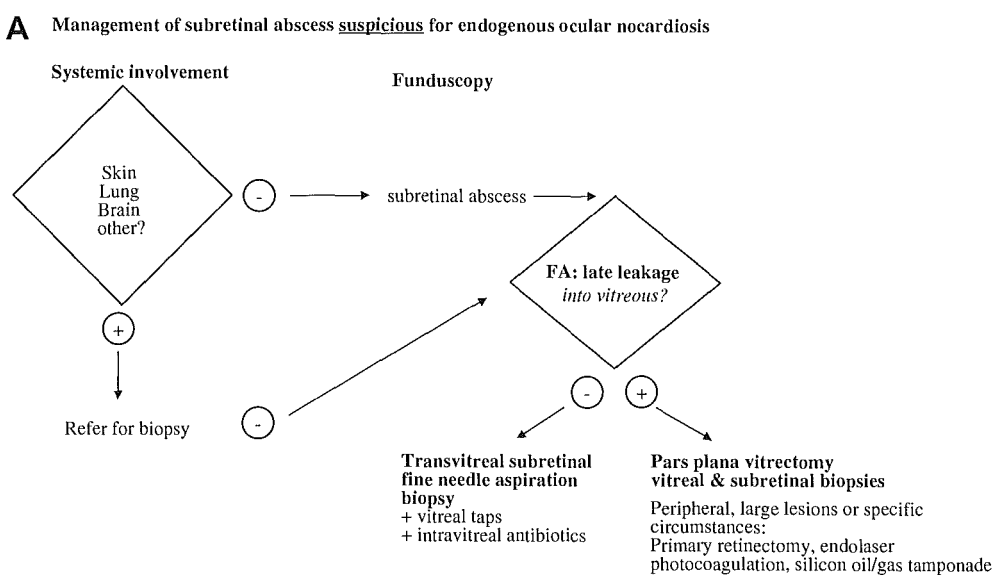

Fig. 6. *A*: About half of the patients first present to the ophthalmologist. The flowchart illustrates the algorithm on how to manage a suspected endogenous ocular *Nocardia* infection. The initial question is if the abscess is isolated in the eye or other organs are affected: The skin is involved in about half of the patients and is easy accessible for a diagnostic biopsy. If the abscess is isolated in the eye or biopsy of other organs is not indicated or too risky, diagnostic biopsy should be done in the eye. A fluorescein angiography helps to choose the appropriate technique in function of the layer affected by the infection: penetration into the vitreous is likely if there is late leakage of FA from the mass into the vitreous traducing a disintegrated pigment epithelium. If positive, a diagnostic and therapeutic PPV together with subretinal biopsies should be performed at first. If negative, the infection is at an initial stage, limited to the subretinal space: A transvitreal fine needle aspiration of the chorioretinal lesion and systemic therapy is the preferred option. *B*: The other half of the patients have a non-ocular infection diagnosed and treated elsewhere. The ophthalmologist is asked to evaluate the lesion in the eye. The question is if the abscess is likely to respond to the systemic treatment alone. Again, a fluorescein angiogram should be performed in order to evaluate penetration of *Nocardia* through the outer ocular barrier, especially into the vitreous. If leakage from the mass into the vitreous is present on late frames, at least injection of intravitreal antibiotics or a pars plana vitrectomy should be performed. On long term the patient should be examined periodically in order to catch complications after scarring such as subretinal neovascular membranes or retinal neovessels. FA = fluorescein angiography; OCT = optical coherence tomography; PE = pigment epithelium; PPV = pars plana vitrectomy.

In advanced cases, where *Nocardia* has invaded the vitreous, the ocular prognosis appears to be bleak even with adequate systemic treatment. Such treatment may eliminate *Nocardia* at the level of the choroid, Bruch's membrane, and pigment epithelium, but *Nocardia* persists in the vitreal cavity. Vitritis is not a reliable sign for vitreous involvement, but late leakage of fluorescein from the mass into the vitreous indicates necrosis and a break of the outer blood–ocular barrier with potential vitreal invasion. A PPV, combined with a subretinal biopsy, is probably the best diagnostic and most efficient therapeutic choice in such eyes. Additional retinectomy with eradication of the subretinal abscess, as performed in our patient, is justified in selected cases, depending on the location and extent of the abscess, and on the posterior vitreous if detached or not over the abscess.

I. APPROPRIATE SYSTEMIC ANTIBIOTICS

1. Intraocular Drug Levels Attainable with Systemic or Regional Administration of Antibiotics

A comprehensive summary for systemic therapy and a table of minimal inhibitory concentrations (MIC) values, ranges, and breakpoints was published previously.[82] Ideally, minimal bactericidal concentrations (MBC) should be about tenfold higher to be sure of bactericidal effect[85] in the eye. Instead, often MIC are measured, and MBC are not known. Data on ocular pharmacokinetics are limited. Nevertheless, we try to summarize what is known. Close follow-up will guide therapy.

Nocardia species are classified by their antimicrobial susceptibility patterns.[138] Most *Nocardia* species are susceptible in vitro to sulfonamides (with or without trimethoprim), considered as the treatment of choice for nocardiosis. TM-SMX is the preferred formula because of the general familiarity with the drug. In disseminating disease combined antibiotic treatment should be considered.

In vitro, *N. asteroides complex* (type VI drug susceptibility pattern)[17] consists of sensitivity to ceftriaxone, amikacin, linezolid, and imipenem and resistance to ampicillin, amoxicillin-clavulanic acid, clarithromycin, and ciprofloxacin. *N. farcinica* (type V drug susceptibility pattern), however, is sensitive to ciprofloxacin, linezolid, and imipenem; resistant to aminoglycosides except amikacin; and resistant to ampicillin, broad-spectrum cephalosporins, and clarithromycin. Both are sensitive to amikacin, linezolid, and imipenem; in addition, *N. asteroides complex* is susceptible to ceftriaxone, *N. farcinica* to ciprofloxacin.

For the treatment of cerebral nocardiosis, the addition of at least a cephalosporin (cefuroxime or ceftriaxone) or ciprofloxacin to TM-SMX has been proposed.[82] Another group states that "most clinicians recommend a three-drug regimen consisting of TM-SMX, amikacin, and either ceftriaxone or imipenem for patients with serious disease, CNS disease, and/or disseminated disease [page 271]."[17] It may sometimes be necessary to use other antibiotics (e.g., macrolides, tetracycline), but these drugs are not discussed here.

Sulfonamides and TM-SMX are bacteriostatic by interference with microbial folic acid and purine/DNA synthesis. Recommended treatment for cerebral nocardiosis in adults consists of high-dose intravenous TM (15–20 mg/kg/day) and SMX (75–100 mg/kg/day) for about 6 weeks[79] or TM-SMX 160 mg/800 mg IV every 6 hours or two pills double-strength twice daily[82] followed by 1 year of oral antibiotics in immunocompromized patients. Patients infected by HIV require longterm maintenance therapy. Sulfonamide and TM-SMX both have good CSF penetration. Sulfonamides are metabolized to an inactive component in the liver, metabolized, and free drug is excreted by the kidneys. Dosage must be adapted in renal insufficiency when clearance is below 30 mL/min. Adverse reactions are acute hemolytic anemia, leukopenia, thrombocytopenia, and agranulocytosis. TM-SMX should not be given in patients with known deficiency in folic acid, glucose-6-phosphate dehydrogenase, or known sulfa-allergy. A much higher frequency in adverse reactions—skin rashes, cytopenia, and hepatotoxicity—occurs in patients affected by AIDS. Concomitant use of cyclosporin in kidney transplant enhances its nephrotoxicity. Severe cytopenia may occur with simultaneous use of methotrexate and TM-SMX.

Recently, MIC90 was determined at 1/19 μg/mL (TM/SMX) and MIC ranges ≤0.5/9.5 μg/mL to >2/38 μg/mL of 51 isolates of *Nocardia* spp. [23] with four isolates resistant, two belonging to *N. farcinica* and two to *N. cyriacigeorgica* (formerly *N. asteroides* type VI drug susceptibility pattern).

There are no ocular studies of TM-SMX in double dosages recommended for nocardiosis. Aqueous humor concentrations were measured for usual dosages of TM-SMX. There was 0.25 μg/mL[104] of TM after 1 day, 1.51 μg/mL[111] after 3 days, and 1.37 μg/mL[117] of TM after 7 days in the anterior chamber. SMX was measured at 17.3 μg/mL[104] after 1 day, 13.5 μg/mL after 3 days,[111] and 15.5 μg/mL[117] of free SMX after 7 days in the anterior chamber. In one study,[111] in 2 of 37 samples, liquefied vitreous was present; one sample after a single administration of double strength TM-SMX and one sample after

steady-state equilibrium after three days treatment. Both samples where in harmony with the results of aqueous humor, so that it was concluded that the concentration of TM-SMX at least in the liquefied vitreous are similar to that in aqueous humor.[111]

Intraocular penetration of TM-SMX in rabbit eyes delivered subconjuntivally, retrobulbarly, or single-dose intramuscularly (0.25 mg/0.1 mL; 2.5 mg/mL; 2.5 mg/kg TM-SMX, respectively) was conducted in 1989 for the treatment of toxoplasmosis.[129] Retrobulbar injection obtained the quickest and highest SMX concentration (105 μg/mL) in the anterior chamber, vitreous, and choroid/retina. Intravitreal drug concentrations dramatically declined after 2.5 hours to 5–10 μg/mL, with maintenance of high concentrations at the level of the choroid/retina after 5 hours, endpoint of the study. Intramuscular injection showed a parallel, linear increase of SMX in the anterior chamber and vitreous, with concentrations very much lower than those found after retrobulbar injections (10–20 μg/mL). The increase of concentration in the vitreous was constant for 5 hours. Concentration after 1 hour at the choroid/retina reached 40 μg/mL, where it oscillated for the following 4 hours. In rabbits, at least, SMX given systemically reaches concentrations in the choroids/retina above MIC for *N. asteroides*. Concentrations of SMX in the vitreous are probably too low to be effective on *N. asteroides*. Retrobulbar TM-SMX injections might be beneficial as a loading dose when starting systemic therapy for EON, but is experimental.

Rieder[111] found that the concentration of TM in the aqueous humor was 60–87% and that of SMX 20–26% of plasma concentration. Calculated half-life of the drugs in aqueous humor was 9.7 hours for TM (65% of half-life of plasma) and 20.5 hours for SMX (190% of half-life of plasma). In the plasma, 66% of SMX and 45% of TM are bound to proteins and are thus rendered inactive. SMX entered less rapidly in the aqueous humor and was there twice as long as in plasma, whereas TM entered more quickly into the anterior chamber, but was eliminated about one-third more quickly than in plasma. Intraocular protein binding is dependent on intraocular inflammation and is unpredictable.

In the cases reviewed here, 22% of patients with EON responded to TM-SMX alone, and 16% in combination with other antibiotics. Thirteen percent (13%) of patients did not respond to systemic TM-SMX. Of those with effective systemic treatment, five eyes with vitreal sequestration treated by sulfadiazine, one by sulfisoxazole, and three with TM-SMX did not heal.

Amikacin, an aminoglycoside, has good in vitro susceptibility testing results for most strains of *Nocardia* spp. and is bactericidal. Amikacin has a relative high oto-, neuro-, and nephrotoxicity, which is cumulative; therapy is usually limited to a maximum of 2 weeks. Its penetration into CSF is poor.[82] Intrathecal injection are sometimes necessary.[82]

MIC ranges of amikacin are low, 0.25–4 μg/mL. Intracameral[39] concentrations after a single infusion of amikacin 7.5 mg/kg (half dosage for 24 hours) 30 minutes prior to sampling, topical (15 mg/mL four times every 15 minutes prior to surgery) and subconjunctival (100 mg) were non-detectable after intravenous, very low after topical, and very variable after subconjunctival injection in 15 patients for each route of administration undergoing cataract surgery.

Kasbeer et al[65] studied in 1975 the penetration of intramuscular, topical, and subconjunctival amikacin in the rabbit eye[65] with normal phakic, postoperative aphakic, and aphakic eyes with *Pseudomonas* endophthalmitis.

After a single intramuscular injection of 15 mg/kg amikacin (entire human dose for 24 hours) in rabbits by Kasbeer et al, concentrations in the humor aqueous ranged from 0.2–2.1 μg/mL in the phakic and 1.7–5.1 μg/mL in the aphakic eye 3 to 6 hours after injection. In the posterior vitreous concentrations were lower with 0.1–0.5 μg/mL in the phakic and 0.1–0.9 μg/mL in the aphakic eye. In another study[80] with rabbits, maximal intravitreal concentrations of amikacin after intravenous infusion of amikacin 6 mg/kg twice daily, lensectomy and vitrectomy with inflammation induced by injection of heat-killed *Staphylococcus aureus* reached 8.5 (±3.2) μg/mL.

Kasbeer et al applied eye drops every 5 minutes (10 mg/mL) for 3 hours applying a total of 25 mg. Amikacin ranged in the aqueous humor between 0.7 and 3 μg/mL in the phakic and 0.4–3.2 μg/mL in the aphakic eye. There was 0.1–1.0 μg/mL in the posterior vitreous of phakic and aphakic eyes. Kasbeer et al injected subconjunctival amikacin once at 10 mg. Concentrations in the aqueous were between 0.7 and 7.5 μg/mL in the phakic and 1.3–10 μg/mL in the aphakic eye. In the posterior vitreous drug concentration ranged from 0.1–2.5 μg/mL in the phakic and 0.1–1.5 μg/mL in the aphakic eye. Subconjunctival injection of 25 mg amikacin by Erkin et al[41] resulted in a mean concentration of 9.32 (±2.61) μg/mL in the aqueous.

Combining all three routes by Kasbeer et al, in all compartments the concentrations were considerable higher: In the aqueous humor up to 19 μg/mL

in the phakic and 30 μg/mL in the aphakic eye. Concentrations between 0.6 and 4.7 μg/mL and 0.9–8.3 μg/mL were reached in the posterior vitreous of phakic and aphakic non-infected eye, respectively, and 0.7–4.0 μg/mL in the infected aphakic eye.

Combination therapy was used with success by Tan in a severely inflamed eye of a comatose patient.[128] The patient was treated systemically first by high-dose TM-SMX, later converted to sulfadiazine because of resistance, ceftriaxone, and amikacin and weekly subconjunctival amikacin injections, topical cefuroxime and gentamycin on a hourly basis with tapering to four times daily after 2 weeks. Combining systemic, regional, and topical amikacin seems of value at least as adjunctive therapy in eyes to prevent vitreal sequestration of *Nocardia.* With vitreal invasion, PPV or intravitreal amikacin injections, discussed subsequently, are excellent choices.

Ceftriaxone, a third-generation cephalosporin for parenteral use, is only an option for *N. asteroides.* It is bactericidal and has good CSF penetration. Bacteriostatic antibiotics (sulfonamides) may interfere with the bactericidal effect of ceftriaxone. There is physical incompatibility with aminoglycoside, so that infusions must be given separately, but there is synergism with aminogylcosides. MIC for *N. asteroides sensu stricto* are 2 and 8 μg/mL, for MIC50 and MIC90,[82] respectively. Intravitreal concentrations in patients undergoing surgery for retinal detachments and other issues, were 5.9 (±5.5) μg/mL measured with high performance liquid chromatography (HPLC) and 11.5 (±9) μg/mL by bioassay measured after 48 hours 2g twice daily intramuscular administration. Some patients were already vitrectomized, one aphakic patient had the highest intravitreal concentration (28 μg/mL bioassay).[122]

Ciprofloxacin, a fluoroquinolone that is bactericidal, is only to be considered for infections with *N. farcinica.* The MIC of *N. farcinica* ranges between 0.25 and 8 μg/mL.[82] Thirty-two percent (32%) of *N. farcinica* isolates are resistant (100% *N. nova* and 62% of *N. asteroides*). Isolates with MIC 90 > 4 μg/mL are considered resistant.[82] Maximal serum concentration after 400 mg IV infusion was 3.9 mg/L. There is little binding to protein (20–30%) with rapid diffusion into the extracellular space with accumulation in different tissues. Only 6–10% of maximal serum concentration passes in the CSF. Dosage has to be adapted in the elderly and in patients with reduced renal clearance. A single dose of 750 mg ciprofloxacin resulted in vitreal concentration of 0.19 μg/mL.[66] Two doses yielded mean concentrations of 0.51–0.56 μg/mL,[66,75] more or less equal to a single administration of 1000 mg with 0.64 μg/mL.[22] Subretinal fluid analysis demonstrated 0.74 μg/mL ciprofloxacin after oral, and 1.05 μg/mL after combined oral and intensive topical, application, all analyzed by HPLC. One study[92] combined their own data of intraocular ciprofloxacin concentrations and used pharmacological models to predict half-lives. The authors estimated a vitreous half-life of 5.3 hours. With dosages of ciprofloxacin 750 mg every 6 hours, they found vitreous concentrations of 1.0 μg/mL (±0.45), with about 15% of patient still having concentration below 0.5 μg/mL. In a rabbit eye model with *Staphylococcus*-induced inflammation, the investigators[98] found a mean vitreal concentration of 1.98 μg/mL with 40 mg/kg ciprofloxacin administration (double dosage) in two doses.

Nemonoxacin—a novel non-fluorinated quinolone—had MIC ranges of 0.03–8 μg/mL with MIC90 at 2 μg/mL on *Nocardia* spp. (19 isolates including three *N. farcinica* and other unusual species). To our knowledge, there are no ocular studies with this antibiotic published.

Imipenem[1] is a beta-lactam with very broad spectrum even on bacteria resistant to other beta-lactams. Imipenem showed the best activity against 51 isolates among the carbapenems, with meropenem being fourfold less active and ertapenem being 16-fold less active than imipenem,[23] whereas in another study imipenem, doripenem, and meropenem were comparable.[73] It is bactericidal by inhibition of cell wall synthesis of Gram-positive, Gram-negative, anaerobe, and aerobe microorganisms. However, its penetration in CSF is around 1–20% of serum levels. MIC90[82] for *N. asteroides sensu stricto* and *N. farcinica* are around 32 μg/mL with a range <0.5 to >32 μg/mL. Its ocular penetration has been studied after single dosage of 1 g intravenously 2–4 hours before vitrectomy: 2 μg/mL[8] to 2.5 μg/mL[2] were measured by microbiologic disk agar technique in eyes of patients with diabetic retinopathy and retinal detachment with proliferative vitreoretinopathy. One of Axelrod's patients had endophthalmitis caused by *Staphylococcus epidermidis* after cataract extraction.[8] She received therapy for 4 days prior to surgery. The vitreal concentration was much higher than a single dose administration at 12.74 μg/mL. Amikacin and imipenem both have unreliable CSF penetration; however, they are synergistic with TM-SMX.[82]

Linezolid, the first oxazolidinone approved in the United States in 2000 by the Food and Drug Administration for <28-day treatments of infections with resistant germs such as methicillin-resistant *Staphylococcus,* seems a logical option for the treatment of nocardiosis because of its excellent in vitro qualities with inhibition of growth of most *Nocardia* spp. with low MIC ranges (0.12–1 μg/mL;[23]

≤0.25–8 μg/mL;[18] 0.5–16 μg/mL[73]). Its activity is directed against the 50S ribosomal subunit, specifically to the 23S component, and inhibits initiation of protein synthesis.[135] The site of binding is close to that of chloramphenicol. Aqueous humor concentrations in the non-inflamed human eye after a single oral dose of 600 mg linezolid was 3.4 (±1.9) μg/mL measured one hour after ingestion.[107] Concentrations raised to 3.9 (±1.1) μg/mL after two hours, to reach maximum concentrations between two and four hours after intake at 6.8 (±1.2) μg/mL, to decline to 3.9 (±1.6) μg/mL after 4 to 8 hours.[107] Comparable concentrations were reached after ingestion of two oral doses of 600 mg at 12-hour interval with 6.6 (±2.7) μg/mL sampled 18 hours after the first dose[48] and after single intravenous infusion of 600 mg linezolid 5.17 (±0.95) μg/mL retrieved 2–4.5 hours after the end of the infusion.[134] Vitreal concentrations after a single oral dose of 600 mg linezolid were 1.25 μg/mL measured 2–3.5 hours after ingestion.[25] Fiscella et al[48] found 2.34 (±1.4) μg/mL after a mean time of 3.5 hours, in the same conditions; and higher concentrations after two oral doses of 600 mg 12 hours apart, taken 18 hours after the first dose with 5.75 (±2.7) μg/mL. Horcajada et al[56] prolonged the interval of sample taking to 24 hours and found 4.5 (±0.8) μg/mL, pointing to an accumulation in the vitreous. They also measured intravitreal concentrations after intravenous infusion of 600 mg linezolid 1, 2, 4, 8, and 12 hours after infusion, where 1.0 (±0.06) μg/mL, 2.2 (±2.0) μg/mL, 3.4 (±1.1) μg/mL, 3.7 (±1.4) μg/mL, and 2.4 (±0.4) μg/mL were found, respectively. (All measurements were done by HPLC). Linezolid was recently used in combination therapy in a patient with EON[136] (published after this review's inclusion period) with a history of systemic lupus erythematosus with repeated kidney transplantation on oral prednisone, cyclosporin, and mycophenolate mofetile. The subretinal abscess was stable under TM-SMX (2 × 960 mg/day) and linezolid (2 × 600 mg/day), later linezolid alone 4 × 600 mg (TM-SMX interrupted for anemia and thrombocytopenia). Brain lesions indeed progressed and warranted an intensification of therapy with ampicillin, sulbactam, amikacin, imipenem, and cilastin. "Two years after treatment, the ocular lesion remains stable and inactive [page 381]."[136]

Linezolid in its oral form has high bioavailability and is comparably well tolerated for 2-week courses. However, with prolonged regimens (>28 days to 3–4 months) linezolid may lead to reversible myelosuppression (45%) that progresses 2 weeks beyond intake. By a probable action on mammalian mitochondria, linezolid is neurotoxic in 18% of cases leading to irreversible peripheral neuropathy. Bilateral, symmetric, painless optic neuritis, mostly reversible, may occur[115] on prolonged treatments (120–1505 days; median duration, 280 days). Decreased visual acuities, sluggish reactive pupils without a relative afferent pupillary defect, optic disc edema, pallor or normal appearance, caecocentral and/or arcuate scotomata with impaired color vision, extinguished visual potential using the 20/50 check size, and increased retinal nerve fiber layer around the optic disk characterize this optic neuropathy.[60,84] Because of its serious side effects on long-term therapy,[61] linezolid was relegated to salvage therapy in a recent review questioning its utility in the treatment of nocardiosis.

A new antibiotic, tigecycline (a glycylcycline, a derivate from minocycline, blocking 30S ribosome) was found to have MIC ranges of ≤0.06 to 4 μg/mL for *N. cyriacigeorgica* in one study.[23] It was active against imipenem-resistant and TM-SMX-resistant isolates. A study from Taiwan found slightly higher MIC ranges (0.12–8 μg/mL;[73] MIC90 at 4 μg/mL) for *N. asteroides*. To our knowledge, there have been no ocular studies for tigecycline to date.

In conclusion, depending on disease progress, species, specific resistance pattern, and operative state and inflammation of the eye, the response to systemic therapy will be variable.

J. ADJUNCTIVE INTRAVITREAL ANTIBIOTICS

Intravitreal 400 μg amikacin injections were used as adjuncts to systemic treatment in one patient with EON[101] when the ocular lesions enlarged while brain abscesses regressed. In another patient,[100] *Nocardia* was found in the necrotic mass of an enucleated eye after repeated intravitreal amikacin injection. Viability was not tested.

Arguments in favor of intravitreal amikacin injections are that the MIC is very low (*N. asteroides complexes*, 0.25–4 μg/mL), the MBC is close to MIC,[85] there are so far no resistant isolates for these species,[82] and intravitreal amikacin is already widely used in clinical practice. Intravitreal amikacin risks inducing macular ischemia. A 400-μg injection of amikacin gives a theoretical intravitreal concentration of 100 μg/mL that is 25 times greater than the MIC90 for amikacin. Clearance of amikacin occurs by the anterior route, and inflammation enhances it clearance. Different clearance rates have been found for variable states of eyes in the rabbit[80,85] (normal, phakic, and aphakic with inflammation, etc.). Maurice[85] estimated that the half-life of a drug in a human eye is 1.7 times that of a rabbit. Four to five half-lives will bring the initial intravitreal concentrations of about 100 μg/mL down to 3–6 μg/mL, still above the MIC range of *N. asteroides*

complex. Four to five half-lives corresponds to between 2 and 9 days, depending on the operative/inflamed state of the eye, calculated in Table 7.

In regards to toxicity, a single dose of 1500 μg amikacin produced retinal toxicity in the rabbit eye,[32] corresponding theoretically to a concentration of around 1000 μg/mL (rabbit vitreous, 1.4–1.7mL) that is 10 times the concentration found in humans (400 μg in 4 mL). Toxicity may be reached with smaller, repeated injections of 400 μg, as shown after three injections given at 48-hour intervals in the rabbit eye. With a higher volume of distribution in the human eye and prolonged intervals between injections, toxicity may be lower than in the rabbit eye, but remains uncertain.

In rabbit eyes, intravitreal TM-SMX (1600 μg/0.1 mL) was found to be nontoxic 2 weeks after its administration as shown by histology and electroretinogram (ERG).[47] With this dose, a theoretical concentration of 373 mg/L TM and 1865 mg/L SMX would be achieved in the human eye, assuming that the vitreal volume is about 4.2 mL. This exceeds the MIC of *N. asteroides* by far (TM, <2 mg/L; SMX, 38 mg/L). However, TM-SMX is bacteriostatic and commercially available TM-SMX is in a fixed ratio of 1:5.

In rabbits, intravitreal 2-mg ceftriaxone injection in normal eyes resulted in 445 μg/mL concentration 8 hours and 17.6 μg/mL (±1.4) 72 hours after injection.[124] This corresponds to a theoretical concentration in human eye of 159 μg/mL and 6.28 μg/mL (rabbit vitreal volume:human, 1:2.8[85]; MIC90 *N. asteroides sensu stricto* 8 μg/mL, *N. nova* 16 μg/mL). In rabbits, dosages >7.5 mg altered ERG transiently for 1 week, and dosages >20 mg affected retinal architecture. In monkeys, the same dose of 2-mg ceftriaxone resulted in intravitreal concentrations of 609 μg/mL at 0 hours, 434 μg/mL at 1 day, and 19 μg/mL at 100 hours,[10] which are higher than the calculated human drug concentrations. There was no toxicity noted by ERG or histology.

In rabbits, intravitreal injection of 0.98 mg imipenem (=2-mg tienam in 0.1 mL) was not toxic as shown by ERG, visual evoked potential, and histology at repeated exams for 6 weeks. The authors estimated an intravitreal concentration of 0.65 mg/mL, which would correspond in humans to 230 μg/mL,—seven times greater than MIC90 for *N. asteroides* and *N. farcinica*.[77]

K. ROLE OF SURGERY

The role of surgery is illustrated in Figs. 6A (undiagnosed patient) and 6B (diagnosed and systemically treated patient). In half of all patients the diagnosis of disseminated infection by *Nocardia* was already established when eyes were involved. As discussed earlier, the response of infectious foci elsewhere in the body to systemic antibiotics is not an indicator of their ocular efficacy. Multiple small choroidal lesions are likely to heal with systemic treatment alone. Their increase in size and confluence, however, indicates progression. A break through the retinal pigment epithelium, best detected by FA or OCT, should prompt injection of intravitreal antibiotics or surgical management, as intravitreal sequestration of *Nocardia* is unlikely to heal by systemic treatment alone. Vitrectomy not only decreases the bacterial load, but also enhances antibiotic penetration. In our patient, where the posterior pole was spared, removal of infected retina and subretinal abscess by a retinectomy and silicone oil tamponade resulted in an excellent visual and anatomical outcome. The importance of a relatively aggressive surgical approach when dealing with endogenous endophthalmitis and a subretinal abscess has also been emphasized by Harris et al[53] and Yoon et al[147] in *Klebsiella pneumoniae* subretinal abscesses—both reporting encouraging postoperative results while dealing with a quick-cycling microbe with fulminant disease. In summary, surgery in EON may be warranted in the absence of a therapeutic response to systemic antibiotics, and in the presence of bacterial sequestration in the vitreous.

L. PROPOSED MANAGEMENT OF EON

Our study and other reports emphasize that the most important initial step is the suspicion of nocardiosis based on the patient's risk factors and clinical picture. Figure 6A illustrates the management of an undiagnosed patient. A physical examination should be complemented with a lung CT scan (except with history of trauma or surgery) and a brain MRI, even in the absence of clinical symptoms. Other investigations are undertaken based upon the clinical picture. Tissue biopsies are the initial steps to identify the causative agent and ensure successful treatment: extraocular where available or transvitreal subretinal fine-needle biopsy in small or macular lesions with intact outer ocular barrier, vitrectomy with disrupted outer ocular barrier combined with subretinal biopsy in macular lesion, and/or retinectomy and silicone oil tamponade in peripheral lesions. Direct stains, cultures incubated for at least 2–4 weeks, and PCR studies enhance diagnosis.

Choice and dosage of systemic antibiotics should be made in collaboration with the infectious disease specialist. Systemic steroids and chemotherapeutic agents decreasing cellular immunity should be

reduced as much as possible. Close ophthalmic follow-up with repeated FA and/or OCT is advisable.

Figure 6B illustrates the management after diagnosis to evaluate the probability of success of conservative treatment alone to treat the eye lesions. Intravitreal antibiotics or vitreoretinal surgery is indicated when the vitreous is invaded. Prolonged follow-up is important for the early detection of treatable complications such as cataract, glaucoma, retinal detachment, retinal neovascularization, and choroidal neovascular membranes.

VI. Conclusion

Half of the patients presented first with ocular symptoms. Insidious painless loss of vision caused by chorioretinal infiltrates or a mass lesion with overlying hemorrhages in the macular region with a relative mild inflammatory reaction is typical for EON. *Nocardia* either progresses inwards with vitreal sequestration or outwards causing perforation. Signs of severity that exteriorization is imminent are severe ocular pain with either proptosis or a hypopyon—or with both.

A biopsy for adequate microbiology is crucial, either from an easily accessible extraocular site or from the eye. Transvitreal subretinal fine-needle biopsy and PPV with subretinal biopsy have the greatest chance to deliver a significant specimen. Systemic antibiotics and tapering steroids are the pillars of treatment completed by regional antibiotics and surgery.

VII. Method of Literature Search

A literature search of case reports of endogenous ocular *Nocardia* was conducted using OVID Medline (1950–2007), EMBASE by meshing keywords *Nocardia/ nocardiosis* and *eye, ocular, endogenous, endophthalmitis, subretinal abscess, uveitis.* Additional manual searches were conducted by using Index Medicus (1888–1917), Quarterly Cumulative Index Medicus (1917–1950), Excerpta Medica (1947–1966), Ophthalmic Literature (1947–1966), Zentralblatt für die Gesamte Ophthalmologie und ihre Grenzgebiete (1914–1966), and Centralblatt für praktische Augenheilkunde (1888–1919) searching for *Nocardia, Streptothrix, Cladothrix, Proactinomyces* (previous terms for *Nocardia*). Exogenous cases of ocular nocardiosis such as after ocular trauma or ocular surgery were excluded. When EON was present as shown by the clinical picture/microbiology of eye and/or other organs, the case report was included, irrespective of the language of publication. Two patients' histories[9,15,52,70] were reported twice by different groups (ophthalmologists and internists): The data from the correlating field were retained when not homogenously reported (data for systemic history from the internist group, data for the ocular history from the the ophthalmologist group), with exception when something was not stated by one group.

Case reports span the time period from 1967 to 2007.

VIII. Disclosure

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A. www.dsmz.de/microorganisms/bacterial_nomenclature_info.php?genus=Nocardia&show_all_details=1).

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Reprint address: Thomas J. Wolfensberger, MD, PD, MER, Jules Gonin Eye Hospital, 15 Av. de France, CH-1000 Lausanne 7, Switzerland. e-mail: thomas.wolfensberger@fa2.ch.

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