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BRIEF REPORT

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Lymphomatoid granulomatosis in a renal transplant patient

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Abstract Lymphomatoid granulomatosis is a rare angiocentric and angiodestructive pulmonary angiitis considered as a variant of the lymphoproliferative disorder group. Patients with organ transplantation are at an increased risk for post-transplant lymphoproliferative disorders secondary to their immunosuppression. However, lymphomatoid granulomatosis has rarely been described in patients with renal transplantation. It often presents with severe pulmonary signs. We describe a case whose initial presentation was an isolated VIth nerve palsy. We review the radiological and pathological findings and discuss the etiopathogenesis and therapeutic options of this particular lymphoproliferative disorder. With careful and stepwise reduction in her immunosuppression, our patient showed a complete disappearance of her lymphomatoid granulomatosis, and she is clinically well more than 3 years after the diagnosis, with good kidney function.

Keywords Lymphomatoid granulomatosis · Kidney transplantation · Immunosuppression · Drug side effect

Introduction

Lymphomatoid granulomatosis (LGY), an angiocentric and angiodestructive pulmonary angiitis, is considered as a variant of the lymphoproliferative disorders. Patients with organ transplantation are at increased risk for post-transplant lymphoproliferative disorders (PTLD) secondary to their immunosuppression. Although PTLD is a well-known complication of immunosuppression, LGY has rarely been described after renal transplantation. We report the unusual initial neurological manifestation of a cerebral LGY in a patient with a renal transplant. We review the radiological and pathological findings and discuss the etiopathogenesis and therapeutic options of this particular lymphoproliferative disorder.

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Case report

A 16-year-old girl was referred to the renal unit with terminal renal failure secondary to systemic lupus erythematosus (SLE). She was dialyzed for 6 months before receiving her mother's kidney. The donor was Epstein-Barr virus (EBV) positive (IgG VCA IF positive, EBNA AC IF positive, IgM VCA IF negative), whereas the recipient was EBV negative. Immediate post-transplant evolution was remarkable for two rejection episodes, treated with methylprednisolone (500 mg i.v. x2 daily), and a stenosis of the transplanted ureter, which needed surgical correction.

Nine months after transplantation she presented with an isolated left abducens nerve palsy. At that time she was receiving cyclosporine A (200 mg p.o. twice daily, targeted whole-blood monoclonal cyclosporine A level 200 ng/ml, TDX whole blood), prednisone (30 mg p.o. daily), and mycophenolate mofetil (MMF) (600 mg/m^2 per dose p.o. twice daily). Differential diagnosis of an isolated VIth nerve palsy includes trauma, cerebral tumors, immunological disorders (SLE, multiple sclerosis), and infections (sinusitis, cerebral abscess, Lyme disease) [1, 2, 3]. Magnetic resonance imaging (MRI) of the central nervous system (CNS) was normal. SLE was inactive, as assessed by a normal C3 and C4 and no increase in her antinuclear antibody titer. Antiphospholipid antibodies were absent. Coagulation profile and complete blood count were normal. Cerebrospinal fluid (CSF) showed an increased protein concentration (730 mg/l) and hypercellularity (77 white cells, 90% lymphocytes, and no lymphomatous cells). Borrelia Burgdorferii antibodies, antinuclear antibodies, and p-cANCA were negative in the plasma and in the CSF. Two weeks later her neurological status worsened, with the development of a left peripheral facial palsy with discrete left hypoesthesia in the fifth nerve territory. CNS imaging [computed tomographic (CT) scan] was again normal.

One month after initial presentation, a new cerebral MRI showed for the first time a right frontal posterior hyperintense (T_2-weighted images) lesion (Fig. 1) with surrounding edema. There

Table 1 Differential diagnosis of a hyperintense cortical cerebral lesion with accompanying vasculitis

Infectious process	Actinomycosis, aspergillosis, coccidioidomycosis, herpes simplex infection, syphilis infection
Tumors	Lymphomatoid granulomatosis, lymphoma
Collagen vascular disease	Systemic lupus erythematosus
Granulomatous angiitis	Lymphomatoid granulomatosis, Wegener disease, sarcoidosis

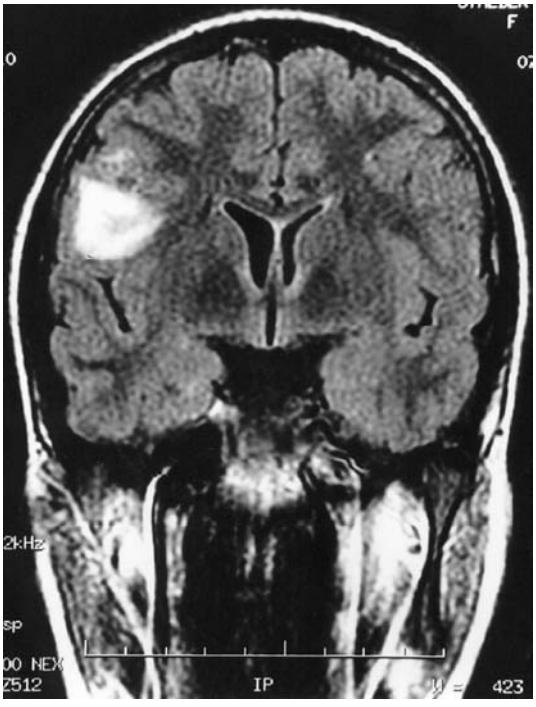

Fig. 1 Brain magnetic resonance imaging shows a high-intensity lesion in the right posterior area of the frontal cortex

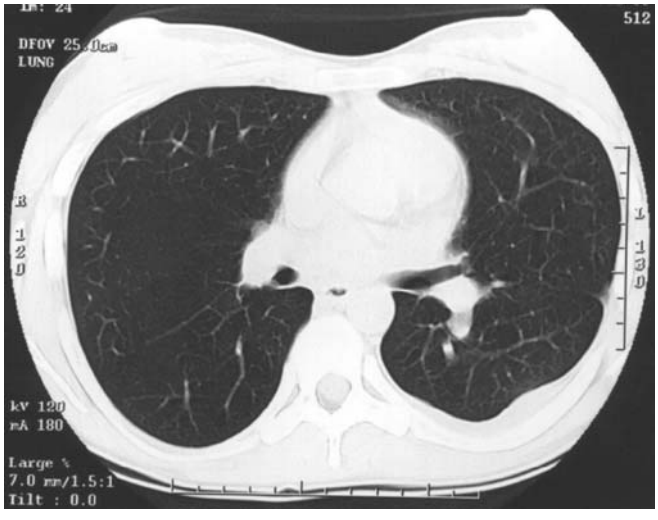

Fig. 2 Computed tomographic scan of the chest shows a localized thickening of the left posterior pleura, with lung parenchyma of normal appearance

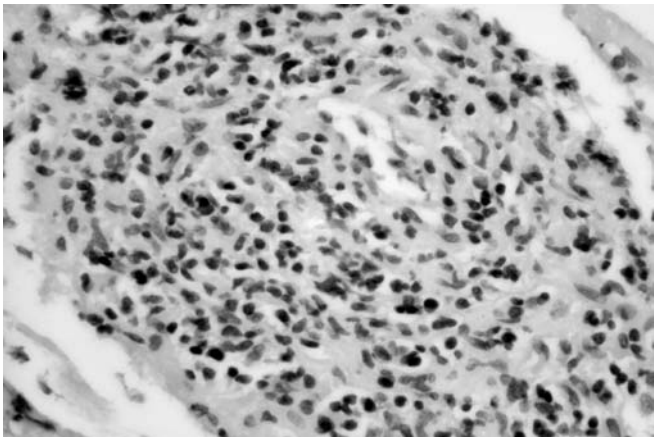

Fig. 3 Histological representation of the pleural lesion. A mixed type of inflammatory infiltrate made up of lymphocytes, plasma cells, and histiocytes surrounding and infiltrating a vessel wall is shown. Hematoxylin and eosin ×400

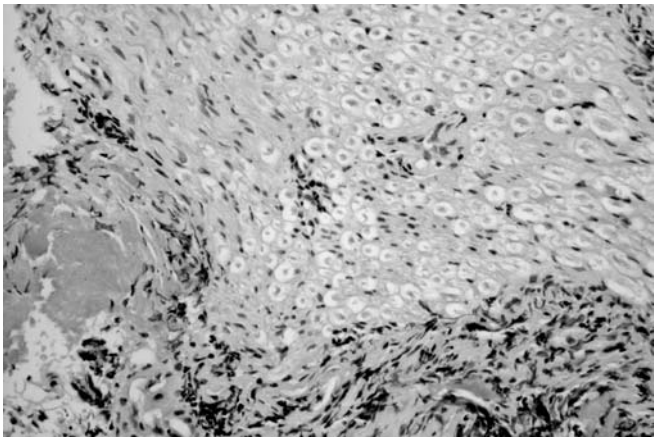

Fig. 4 Segment of nerve infiltrated in the perineurium by the same type of mixed inflammatory infiltrate as seen in some of the vessels. Hematoxylin and eosin ×400

was also an important inflammation of the left basis of the cranium (left jugular foramen, internal auditory canal, VIth nerve territory), the left periventricular area, and the right and left choroid plexus. Differential diagnosis of a cerebral mass with vasculitis includes tumoral, infectious, or immunological causes (Table 1). Serology for varicella-zoster, herpes zoster, and toxoplasmosis was negative, or did not show any acute infection. The patient was still seronegative for EBV. Lumbar puncture was abnormal again, with decreasing hypercellularity and protein. Ziehl and cultures for bacteria, mycobacteria, fungi, and parasites were negative. CSF polymerase chain reaction (PCR) for mycobacterium tuberculosis was negative, but positive for EBV. Converting enzyme activity was within normal limits. Due to the location of the cerebral mass, the neurosurgeon considered a biopsy to be too risky. Cerebral lymphoma or abscess following immunosuppression was the most likely diagnosis.

Meanwhile she complained for the first time of posterior chest pain. Chest X-ray was normal, but a CT scan showed a localized thickening of the left pleura (Fig. 2). The pleura biopsy (Figs. 3 and 4) showed multiple foci of severe inflammatory reaction with

a mixed cell type, including lymphocytes, a few large atypical cells, plasma cells, macrophages, and multinucleated giant cells forming a granulomatous reaction. Numerous blood vessels presented extensive vasculitis. Perineural infiltration by inflammatory cells was present (Fig. 4). Focally, necrosis was a prominent feature and numerous blood vessels were obstructed by microthrombi. Immunohistochemistry showed the inflammation to be made up of small T cells (CD3+) surrounded by foci of rare B cells (CD20+, IgG+). There were no morphological criteria for malignancy. A rearrangement study for the T cell receptor (TCR) gene (T cells), as well as search for clonal rearrangement of the IgH chain gene (B cells) by Southern blot, failed to reveal any monoclonality. In situ hybridization for EBV (EBER 1/2) in the pleural biopsy material was negative. This histological picture of a polymorphous and granulomatous type of inflammatory reaction centered around vessels with nerve involvement, necrosis, and various numbers of large atypical cells was highly suggestive for the diagnosis of an LGY following immunosuppression.

Cyclosporin A and MMF were decreased by 50%, and prednisone increased up to 60 mg daily p.o. for about 1 month. MMF was then stopped altogether and prednisone gradually decreased. Three years later the patient still has a functioning renal graft, on prednisone 5 mg/day and cyclosporin A 100 mg twice daily p.o.. The left VIth nerve palsy has completely resolved, and the left facial palsy improved dramatically. The patient seroconverted for EBV (IgG VCA IF positive, EBNA AC IF negative, IgM VCA IF negative) more than a year after transplantation, once immunosuppression was minimal, without any clinical symptoms.

Discussion

LGY is an atypical angiocentric and angiodestructive lymphoproliferative disease involving primarily the lungs as well as other extranodal sites. Since its first description by Liebow in 1972, LGY has been reported worldwide, mainly in the adult medical literature [4, 5, 6]. Although patients of all ages may be affected, LGY is a very rare entity in pediatric patients: only 12 patients out of 152 described by Katzenstein et al. [5] were less than 20 years old. Since then pediatric cases have been sporadically reported [7, 8, 9, 10]. LGY shows an increased incidence with age, most cases occurring between the 4th and 5th decade. A variety of diseases are associated with LGY, such as lymphoma, acute lymphoblastic leukemia, chronic lymphatic leukemia, breast or colonic carcinoma, sarcoidois, infectious hepatitis, congenital immunodeficiencies, or AIDS [4, 5, 6, 11, 12, 13, 14, 15, 16]. Amongst all those factors, immunodeficiency, either congenital or acquired, is the most frequent and important risk factor. Immunosuppression can induce both PTLD and LGY via impaired T cell surveillance, chronic cytomegalovirus and/or EBV infections, increased B cell interleukin production, and activation of specific cellular oncogenes such as *bcl* 2 [17]. Chronic EBV infection is probably the most important single event in the development of PTLD and LGY, through activation of proto-oncogenes or surviving genes. The EBV genome is detected in most PTLD and LGY biopsy material by PCR, Southern blotting, or in situ hybridization [17]. The finding of one PCR positive for EBV in the CSF of our patient, with negative studies on the biopsy material, is somewhat surprising. Negative findings in the biopsy material might reflect technical problems in retrieving the EBV genome from the rather rare infected B cells. Despite immunosuppression inherent to any organ transplantation, LGY has only rarely been described after either renal [18, 19, 20, 21], heart-lung [22], or bone marrow [23] transplantation.

Clinically, patients with PTLD or LGY present with general signs and symptoms, such as fever, malaise, and weight loss. The majority of patients with LGY complain of dyspnea, cough, or hemoptisis [6], whereas PTLD often manifests itself with adenopathies in the head and neck area and/or tonsillar enlargement [17], less commonly with gastrointestinal, liver, spleen, allograft, lung, or CNS involvement [24]. In the studies of Srivastava et al. [17] and Cockfield et al. [25] none of the patients with PTLD developed pulmonary lesions, and only one of eight patients in the study of Ho et al. [24]. This is in sharp contrast to LGY: more than 70% of patients with LGY have major pulmonary complaints and/or an abnormal chest X-ray.

CNS involvement is present in 22% of patients with post-transplant non-Hodgkin lymphoma. In 55%, the lesion is confined to the CNS, whereas 45% of patients had involvement of other organs [26]. In one study, isolated CNS tumors in transplant recipients without pulmonary involvement were mainly represented by lymphoma, with large cell lymphoma, B cell lymphoma, unspecified lymphoma, and PTLD representing 39%, 28%, 2%, and 4% of all CNS lymphomas, respectively [26]. CNS involvement in LGY is also common, affecting about 20%–40% of patients [5, 6]. Mostly, cerebral involvement follows severe pulmonary disease. Isolated CNS involvement of LGY is rare [9. 10, 27, 28, 29, 30, 31, 32]. Cerebral lesions of LGY are often located in the posterior fossa and commonly present a necrotic or hemorrhagic center secondary to thrombosis of the involved vessels [33]. Two observations should strongly favor the diagnosis of cerebral LGY over cerebral PTLD: the association of a cerebral mass with extensive pulmonary involvement and/or with cerebral vasculitis. CNS involvement of LGY might produce ataxia, visual field defects, Bell palsy, mononeuritis multiplex, or peripheral neuropathy [34].

Skin involvement is present in 40% of patients with LGY [6]. Patients often have a rash, and skin lesions range from subcutaneous nodules to maculopapular eruptions [5, 6, 10, 22, 34]. Skin is a common site of recurrence after therapy of LGY, making careful dermatological follow-up a means of monitoring the disease. PTLD less frequently affects the skin and mostly presents as a nodular painless mass.

From a radiological point of view, it is extremely difficult to differentiate between PTLD, LGY, or non-Hodgkin lymphoma. In the chest, PTLD is characterized by the presence of discrete solitary or multiple nodules [35]. Less frequently, diffuse parenchymal infiltration may also be seen. The pulmonary abnormalities in LGY are most often bilateral, poorly defined nodular lesions, predominantly affecting the lung bases or with nonspecific reticulonodular parenchymal infiltration [35]. Those lesions can even form cavities. Enlargement of

mediastinal lymph nodes is uncommon, but pleural effusion may appear in 33% of patients [11, 36]. Cerebral CT scan demonstrates multiple contrast-enhancing parenchymal lesions with edema and a mass effect in both LGY and PTLD [29, 37, 38, 39]. CNS MRI can show the characteristic changes compatible with LGY, as in the study of Ng et al. [29] and in our patient. In LGY, multiple punctuate and linear areas of contrast enhancement are present in the brainstem and white matter and correspond to the inflammatory reaction of the small vessels. A cerebral mass with basal cerebral vasculitis is a characteristic finding in LGY, although it is not exclusive to this disorder [38]. In difficult radiological cases, perfusion MRI can help distinguish between a tumoral process (PTLD, LGY) and an infectious process. In the case of a tumoral process, the mass will show an increased regional cerebral blood flow, whereas reduced regional cerebral blood flow can be seen in abscess and might be secondary to vasoconstriction associated with increased interstitial pressure [40]. This test awaits further confirmation in patients with LGY.

Nodules in LGY have a polymorphous cellular composition and in addition to the lymphocytes, which predominate, include plasma cells, immunoblasts, and scattered histiocytes. Neutrophils, eosinophils, or well-formed granulomas are occasionally seen or absent [6]. Perivascular collection of lymphoid cells may be predominant. Lymphocytes, mainly T cells, may show direct vascular invasion. Analyses of clonal rearrangement of the TCR have often been either completely negative or have demonstrated unusual rearrangement not seen in T cell lymphoma. The fact that B cells in LGY can present IgH chain gene rearrangement together with chronic expression of the EBV genome suggests B cells as the origin of the process in LGY.

Treatment in LGY and especially in cerebral LGY remains controversial. Most authors agree that LGY arising after organ transplantation should be first treated with diminishing immunosuppression, as in PTLD. There is no specific therapy and most cases reported in the literature to date are anecdotal. In the case of progressive disease, conventional chemotherapy should be tried first [41]. The use of interferon-α2b [42, 43] or radiotherapy [44, 45] has been reported with varying degrees of success in the adult literature. In a patient with multiple relapses, bone marrow transplantation has been used successfully [8]. Therapy should be directed at present on a case-by-case basis, depending on the degree of local or systemic involvement. The fact that our patient responded well to a decrease in immunosuppression likened LGY to the PTLD.

In conclusion, LGY after transplantation is rare and often first present with pulmonary signs. We describe a patient where the initial presentation was an isolated VIth nerve palsy with minimal pulmonary involvement. Although LGY might be confused with PTLD, LGY has some unique histological (angiocentric angiodestructive disease) and clinical features (primarily affecting the lungs), possibly making it a specific entity. Due to the lack of knowledge of its causes and biology, treatment remains undefined and still unsatisfactory. A significant decrease in immunosuppression led to the disappearance of all lesions in our patient.

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