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Case report

Thymoma, immunodeficiency, and herpes simplex virus infections

Thymomes, immunodéficience et infections à herpes simplex virus

M. Méan^{a,*}, M.D. Schaller^a, S. Asner^b, P. Meylan^b, J.-L. Pagani^a, P. Tarr^c, P. Eggimann^a

^a Department of intensive care medicine, centre hospitalier universitaire Vaudois, university of Lausanne, route du Bugnon, Lausanne, Switzerland

^b Infectious diseases service, department of medicine, centre hospitalier universitaire Vaudois, university of Lausanne, route du Bugnon, Lausanne, Switzerland

^c Infectious diseases service, Kantonsspital Bruderholz, University of Basel, Bruderholz, Switzerland

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Abstract

Hypogammaglobulinemia develops in 3 to 6% of patients with thymoma and this association is commonly referred to as thymoma with immunodeficiency (formerly Good syndrome). Recurrent infections with encapsulated bacteria and opportunistic infections associated with disorders of both humoral and cell mediated immunity frequently occur in this rare primary, adult-onset immunodeficiency. We report a case of thymoma with immunodeficiency complicated by disseminated herpes simplex virus (HSV) infection and review five additional cases of HSV-related infections reported since 1966 in patients presenting with thymoma with immunodeficiency. Patients presented with epiglottitis, keratitis, recurrent genital herpes, ulcerative dermatitis, and acute hepatitis. Four of the six cases had a fatal outcome, two of which were directly attributable to HSV infection. Since the risk of invasive opportunistic infections is high and the presentation atypical, lymphocyte count and total serum immunoglobulin should be measured regularly in all patients presenting with thymoma with immunodeficiency.

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Keywords: Thymoma; Immunodeficiency; Hypogammaglobulinemia; Disseminated HSV infection

Résumé

Une hypogammaglobulinémie est parfois associée aux thymomes. C'est une immunodéficience primaire, aussi connue sous le nom de syndrome de Good, qui touche principalement les adultes d'âge moyen. Ces patients présentent des déficits de l'immunité humorale et cellulaire avec typiquement des infections à germes encapsulés et opportunistes. Nous rapportons le cas d'une patiente atteinte d'un thymome avec immunodéficience, compliqué d'une infection disséminée à herpes simplex virus. En passant en revue la littérature, cinq autres cas de thymome avec immunodéficience compliqués d'une infection herpétique ont été identifiés, à savoir une épiglottite, une kératite, une infection génitale, une dermatite ulcéreuse et une hépatite aiguë. Quatre patients sur six sont décédés et dans la majorité des cas en raison de l'infection à herpes elle-même. Au vu du risque élevé d'infections opportunistes et de leur présentation atypique, le taux de lymphocytes et d'immunoglobulines devrait être mesuré régulièrement chez tous les patients présentant un thymome avec immunodéficience.

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Mots clés : Thymome ; Immunodéficience ; Hypogammaglobulinémie ; Infection disséminée à HSV

1. Introduction

Hypogammaglobulinemia develops in 3 to 6% of patients with thymoma. This rare association of thymoma and adult

onset immunodeficiency was first reported by Robert Good and colleagues in 1954, and was commonly referred to as Good syndrome. The present International union of immunological societies 2007 classification replaced this old eponym by thymoma with immunodeficiency and lists it as a primary immunodeficiency. Thymoma with immunodeficiency is a combined, humoral and cell mediated immune deficiency disorder characterized by onset in the fifth or sixth decade of life. Recurrent sinopulmonary infections with encapsulated bacteria are

* Corresponding author. Department of internal medicine, centre hospitalier universitaire de Vaudois, university of Lausanne, 1011 Lausanne, Switzerland.
E-mail address: Marie.Mean@chuv.ch (M. Méan).

commonly reported. Patients with this primary immunodeficiency are at increased risk of developing severe opportunistic infections including herpes simplex virus (HSV)-related infections [1]. We report a case of thymoma with immunodeficiency in a patient who developed severe pneumococcal pneumonia complicated by purulent pericarditis and a fatal disseminated HSV-1 infection.

2. Case report

A 61-year-old previously healthy woman was treated in 2005 for a thymoma (Stage II according to Masoaka staging) by thymectomy and radiotherapy. In 2006, chronic diarrhea of unknown etiology occurred despite extensive work-up. In February 2008, she developed a community-acquired pneumonia without improvement after 4 days of moxifloxacin and was hospitalized because of dyspnea. The fine score was 76 points. Blood and sputum cultures were repeatedly negative (during moxifloxacin treatment), but a *Streptococcus pneumoniae* urinary antigen test was positive. Lymphopenia (0.2 G/l) was noted.

The patient initially responded to ceftriaxone 2 g/d, but fever and cough recurred, associated with atrial fibrillation and signs of right cardiac failure. Thoracic CT and echocardiography showed pleural and pericardial effusions. She was transferred to the intensive care unit (ICU) because of cardiac tamponade, and surgical drainage of a constrictive pericarditis was performed under general anesthesia. Criteria for pleural empyema were not met. Pneumococcal pericarditis was confirmed by positive *S. pneumoniae* specific PCR (18,500,000 copies/ml) in the pericardial fluid.

The patient developed an acute respiratory distress syndrome requiring mechanical ventilation, followed by renal and liver function impairment. At that time, she was found to be severely hypogammaglobulinemic, with low levels of IgG (0.45 g/L; normal range, 7.0–14.5 g/L), IgA (0.61 g/L; normal range, 0.71–4.07 g/L), and IgM (0.04 g/L; normal range, 0.34–2.41 g/L). Testing for HIV was negative. High dose intravenous immune globulin (IVIg), 1 g/kg per day, was initiated. Vesicular genital lesions appeared; the vesicular fluid was positive for HSV-2 using specific PCR (2,920,000 copies/ml). Fulminant hepatic failure accompanied by disseminated intravascular coagulation developed. HSV-1 was recovered in hepatic biopsy (HSV-1 specific PCR: 14,300,000 copies/mL of homogenized biopsy material), and in blood (HSV-1 specific PCR: 324,000,000 copies/mL). Bronchoalveolar lavage cells contained viral inclusions. Serum HSV titers were inconclusive (HSV IgG enzyme immunosorbent assay (EIA), 0.7; HSV EIA IgM < 0.5). Type-specific HSV serology, HSV type 1 IgG and HSV type 2 IgG, were both negative. Intravenous acyclovir (7.5 mg/kg per day adapted to continuous venovenous hemofiltration) was started for disseminated HSV infection. Despite antiviral and empiric broad-spectrum antibiotics with aggressive supportive care, multiple organ failure progressed and was ultimately fatal.

The autopsy confirmed the presence of disseminated HSV infection involving the liver and the lungs, based on

the presence of large areas of cellular necrosis and positive HSV-immunohistochemical staining throughout the liver and the lung tissue sections.

3. Methods

We searched the English, French, German, Spanish, and Italian literature using the MEDLINE database from 1999 to March 2008 and additional references from retrieved publications. Search terms included: “Good(’s) syndrome”, “thymoma with immunodeficiency”, “thymoma”, “hypogammaglobulinemia”, “HSV” or “disseminated HSV”. Additional cases were identified through an extended review of all the pathogens reported in 51 patients with thymoma with immunodeficiency, from 1966 to 1999 [1–6]. Reports of HSV-related infections were included if they occurred in patients with documented thymoma and hypogammaglobulinemia and/or B-cell lymphopenia [1]. We excluded cases of HSV-related infection in patients with a thymoma but without known hypogammaglobulinemia.

4. Discussion

Typical features of this case of thymoma with immunodeficiency include the initial presentation in a middle-aged woman within a year after thymectomy, with severe pneumococcal pneumonia and purulent pericarditis. The most commonly documented infectious complications in patients with thymoma with immunodeficiency include recurrent upper and lower respiratory tract infections with encapsulated organisms [1]. The patient also had chronic diarrhea, another common feature of thymoma with immunodeficiency, being reported in approximately half of the patients with this primary immunodeficiency. In the vast majority of cases, no specific etiologic agents are identified [1]. Finally, patients with thymoma with immunodeficiency are susceptible to opportunistic infections, including HSV, CMV VZV, *candida* spp., *Pneumocystis carinii* infection, which may be severe or even fatal [1].

In the most comprehensive published review of infectious complications in 51 reported cases of thymoma with immunodeficiency, HSV infection was recorded in four patients who presented with epiglottitis, keratitis, recurrent genital herpes, and ulcerative dermatitis, respectively [1–5]. We identified one additional case of thymoma with immunodeficiency with HSV infection (Table 1) presenting with fulminant hepatic failure leading to death despite liver transplantation [6]. Among all six cases reviewed here, including our case, the majority of patients ($n=5$) had concomitant upper or lower respiratory tract infections. Four cases had a fatal outcome, but only two of these were directly attributed to HSV infection. In fact, only two cases of visceral HSV infection in patients with thymoma with immunodeficiency have been reported until now, a case of fulminant hepatic failure and the present report of a disseminated HSV infection [6].

Disseminated HSV infection in patients with immunodeficiency is a severe infection, thus, a high index of suspicion and aggressive microbiological or molecular investigations of such lesions are important. In our review, the liver was the most com-

Table 1
Literature review of HSV-related infections in patients with thymoma with immunodeficiency.
Revue de la littérature sur les infections à HSV chez des patients avec thymome et immunodéficience.

Case, reference	Age (yr/sex)	Thymectomy	IVIg substitution	HSV type	Syndrome attributed to HSV	Time after thymectomy	Antiviral treatment	Other concomitant infectious disease	Outcome (or presume cause of death)
Beck S, et al. [2]	61/F	No (autopsy finding)	No	NR	Ulcerative dermatitis	-	No	Upper pulmonary infection	Died, respiratory failure
Gupta S, et al. [3]	Elderly/M	No	Yes	NR	Epiglottitis	-	NR	CMV disease, invasive candidiasis, pneumonia	Died, respiratory failure
Eifferman RA, [4]	78/F	No (biopsy)	No	NR	Keratitis	-	Yes	Purulent sinusitis, chronic bronchitis	NR
Verne GN, et al. [5]	66/M	Yes	No	NR	Recurrent genital infection	Occurred before thymectomy	No	Diarrhoea, chronic bronchitis	Improved, after thymectomy
Biancofiore G, et al. [6]	25/M	Yes	No	1	Acute hepatitis	10 days	Yes	NR	Died, multiorgan failure
Present case	61/F	Yes	Yes	1 + 2	HSV-1 disseminated infection	3 years	Yes	<i>S. pneumoniae</i> pericarditis and pneumonia HSV-2 genital infection	Died, multiorgan failure

NR: not reported.

monly involved internal organ. This is consistent with a recent literature review of disseminated HSV infections in immunocompromised patients, which identified the liver as the most commonly affected organ [7].

In thymoma with immunodeficiency, the clinical presentation of HSV infection is usually atypical, and typical skin lesions are not always present. Thus, the diagnosis of HSV infection, mostly hepatitis, may only be made at autopsy. HSV infection among severely immunocompromised patients may have a fatal outcome, which in part may be due to delayed treatment when typical findings specific to HSV infection, particularly a suggestive rash, are absent [6,8]. Typical findings in patients with HSV hepatitis include fever, leukopenia, elevating liver enzymes, disseminated intravascular coagulation, encephalopathy, and acute renal failure. Fulminant hepatitis due to HSV in immunocompetent patients, whereas uncommon, has also been reported [7,8]. The potentially fatal evolution in healthy adults may be attributed to the absence of immediate consideration of HSV as a pathogen in the differential diagnosis of acute hepatitis [7,8], whereas the severity of HSV infection is markedly increased in patients with hematologic or lymphoreticular malignancies and after solid-organ or bone marrow transplantation, even if treated appropriately [7].

Since testing for HSV was inconclusive, it was not possible to discriminate between a diagnosis of HSV reactivation or primary HSV infection. In the setting of hypogammaglobulinemia, antibody-level increase may have been delayed or falsely negative. In a 61-year-old, immunosuppressed and critically ill patient, HSV reactivation seems more likely than primary HSV infection. Furthermore, in the present case, we hypothesized that a primary HSV-2 infection reactivated an old HSV-1 infection (or vice versa), which then caused this fatal invasive infection. In immunocompromised patients, we rarely observe high titers of HSV virions in blood correlated to the almost complete absence of antiherpetic neutralizing and opsonizing function. On one hand, the lack of antibodies increase the odds to detect viremia and widespread disease, on the other hand, the lack of cytotoxic T-cell function increases the risk of an invasive disease. Antibodies may protect from viremia and also play an additional role in protecting from recurrent herpetic infection. In cases of thymoma with immunodeficiency all these may be simultaneously compromised, especially if hypogammaglobulinemia is not diagnosed and IVIg substitution not initiated.

In our case, acyclovir therapy was initiated with a considerable delay; the HSV-positive PCR result of the hepatic biopsy was available approximately one week after the onset of hepatic impairment. This delay may have contributed to the ultimately fatal outcome. Nevertheless, HSV hepatitis has been associated with a poor prognosis in immunocompromised patients, even when effective antiviral treatment is rapidly provided [8]. In this context, it is important to point out that thymoma with immunodeficiency is a combined humoral and cellular immunodeficiency, the typical features being hypogammaglobulinemia and few or no B-cells in the peripheral blood [9]. The CD4+: CD8+ T-cell ratio may be inverted, due to CD4 T-cell lymphopenia [9]. In contrast to thymoma with immunodeficiency, common variable immunodeficiency (CVID), which is

also characterized by hypogammaglobulinemia, is associated with less frequent and less severe cellular immunodeficiency, and fewer opportunistic infections including HSV infection [10]. IVIG substitution is indicated in all patients with thymoma with immunodeficiency, as it may be associated with improved control of infections, decreased use of antibiotics, reduced hospitalizations, and perhaps an improved survival in patients with thymoma with immunodeficiency and other hypogammaglobulinemic conditions [3]. Furthermore, measuring serum IgG, IgA and IgM with the automated methods is easily available. Consequently, since the risk of invasive infections is high and atypical presentation of common and treatable infections are easily missed; all patients with thymoma should have lymphocyte count and quantitative serum immunoglobulin levels measured in order to identify patients in whom IVIG substitution is indicated, usually in the long term [9].

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