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ORIGINAL PAPER

Successful Immunomodulatory Therapy in Castleman Disease with Paraneoplastic Pemphigus Vulgaris

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Abstract Castleman disease is a rare lymphoproliferative disorder. The clinical signs and symptoms of the disease are primarily mediated by cytokines, especially interleukin-6. We presented the case of a young female. In May 2004, a 30-year-old otherwise healthy looking woman presented with oral ulcerations resistant to topical and systemic antibiotic and antimycotic treatment. Bullous mucosal lichen or pemphigus vulgaris were suspected. Histological examination and direct and indirect immunofluorescence confirmed the diagnosis of pemphigus. Search for neoplasm revealed a retroperitoneal Castleman tumour sized 15×6×5 cm in the abdominal MRI. The tumour was a bleeder, so the removal was partial. Histological examination showed hyalin hypervascular Castleman disease. Considering her young, fertile age and the multicentric Castleman disease, non-cytostatic immunomodulatory therapy was started including steroid, cyclosporine-A and thalidomide treatment. The control abdominal CT showed a small residual tumour on the bladder. The residual tumour was removed in repeated surgery. At this time the histological examination showed transient type tumour between plasma cell and vascular variant. Currently, i.e. 4 years after the onset of the disease. ^{18}FDG PET/CT examination showed low metabolic active mass in the right iliacal region, but our patient had no symptoms or complaints. She is on 200 mg thalidomide a day and no tumour progression can be seen. Castleman disease can be successfully treated with non-cytostatic immunomodulatory therapy.

Keywords Castleman disease · Immunmodulatory · PET/CT

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Introduction

Castleman disease (CD) is a rare, atypical lymphoproliferative disorder, which was first described by Castleman et al in 1954 [1]. CD is classified according to the histopathological findings of the affected lymph nodes, the groups being identified as hyaline-vascular, plasma-cell type or a mixed type variant of the two. Furthermore, two clinical types (localised and multicentric) can be distinguished. The hyaline vascular type is the most common histological variant of CD, accounting for 90% of cases. The other 10% consist of the plasmacytoid variant and the mixed type. Patients with the plasma-cell or the mixed-type variant frequently have systemic manifestations, such as low-grade fever, fatigue, loss of appetite, and weight loss [2]. The clinical manifestations are heterogeneous, ranging from asymptomatic disease to severe lymphadenopathy with

severe systemic signs, it can looks like high-grade lymphoma. The prevalence of CD has not been established yet. There are approximately 30.000–100.000 cases in the United States, but there are no data about its European occurrence [3]. The pathogenesis of CD is not clearly understood. Human herpes virus 8 (HHV-8) infection and increased production of interleukin 6 (IL-6) play an important role in pathogenesis. The clinical signs and symptoms of the disease are primarily mediated by cytokines, especially interleukin-6 [2, 3]. Unicentric CD is usually cured after resection or radiotherapy, and has not been associated with increased mortality. Patients with MCD lived as long as several weeks to decades after the diagnosis.

Because of variegation and notably different prognoses of the disease, there is no uniform, evidence-based therapy. The treatment strategies of CD include surgical excision, chemotherapy (like in lymphoma) and radiotherapy. The clinicopathology of the disease is known better and better, so immunmodulators, monoclonal antibodies, and antiviral therapy are also used nowadays. Here we present a unique case of CD with paraneoplastic pemphigus (PNP) and highlight successful treatment and new therapeutic opportunities.

Case Report

In May 2004, a 30-year-old otherwise healthy looking woman presented with oral ulcerations resistant to topical and systemic antibiotic and antimycotic treatment. Her mucosal symptoms werenot accompanied by any skin or eye changes. Bullous mucosal lichen or pemphigus vulgaris were suspected at the first dermatological consultation (Fig. 1). Histological examination of buccal mucosa biopsy with hematoxilin eosin staining showed intercellular oedema, acantholysis in the mucosal epidermis and slight lymphocyte infiltration in the lamina propria (Fig. 2). A direct immunofluorescent examination revealed strong intercellular deposition of IgG and complement three within the mucosal epidermal intercellular spaces. Indirect immunofluorescence confirmed the diagnosis of pemphigus (data not shown).

A regimen of 125 mg intravenous methylprednisolone per day was initiated for 5 days. Then, as the dose was slowly reduced, her symptoms improved. Laboratory examinations revealed hypoalbuminaemia (36 g/l), elevated C reactive protein (CRP: 7,6 mg/l), increased erythrocyte sedimentation rate (28 mm/h) and elevated soluble IL-6 (38,8 pg/ml),. HIV and HHV-8 virus serological tests were negative. Some autoantibodies (for example: ENA, Jo-1) were elevated, but it could be explained by the immunreactive state caused by inflammation. There were no signs that could advert polysystemic autoimmune disease. In searching for neoplasm by vaginal ultrasonography a 133× 32 mm tumour in the pelvic region was revealed. The tumour compressed the urinary bladder. Vaginal ultrasonography demonstrated that it did not affect the ovaries. In the abdominal MRI, a neoplasm of 15×6×5 cm was shown in the right side of the pelvic area (Fig. 3). In addition to the above, inguinal lymphadenomegaly was also found. In March 2005 her CA 125 tumour marker was not elevated. The tumour was thought to be a teratoma. Laparotomy was performed in April 2005. The tumour bled so only a biopsy was taken. The histological examination showed desmoplastic reaction, but did not give a final diagnosis. Each step of the tumour removal was carefully planned. To avoid an increased risk of the operation for the patient on high dose steroid treatment formucosal pemphigus, she was given intravenous immunoglobulin (4×15 g pentaglobin) before the procedure. During secondary laparotomy only part of the neoplasm could be removed because of the high risk of bleeding and involvement of the urinary bladder. The histological examination confirmed hyaline hypervascular Castleman disease (Fig. 4). The patient's young age, lack of

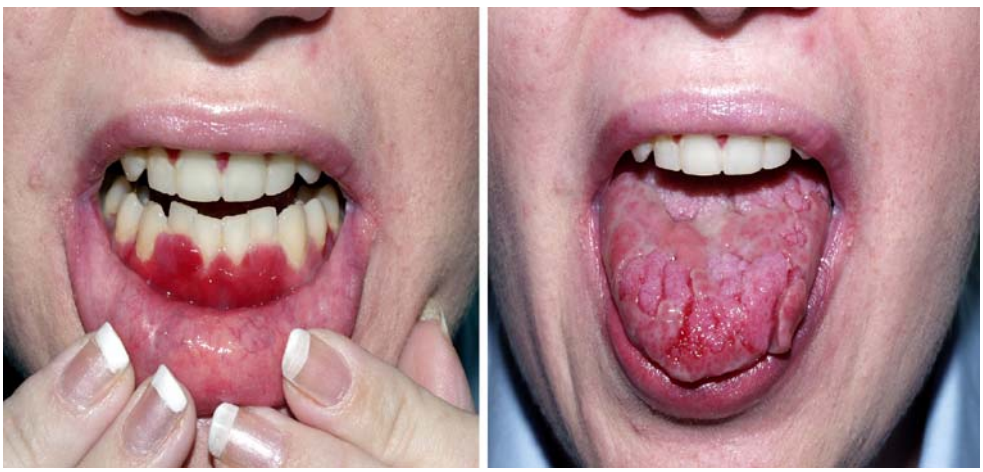

Fig. 1 Gingiva hyperplasia and necrotic lesions on the tongue

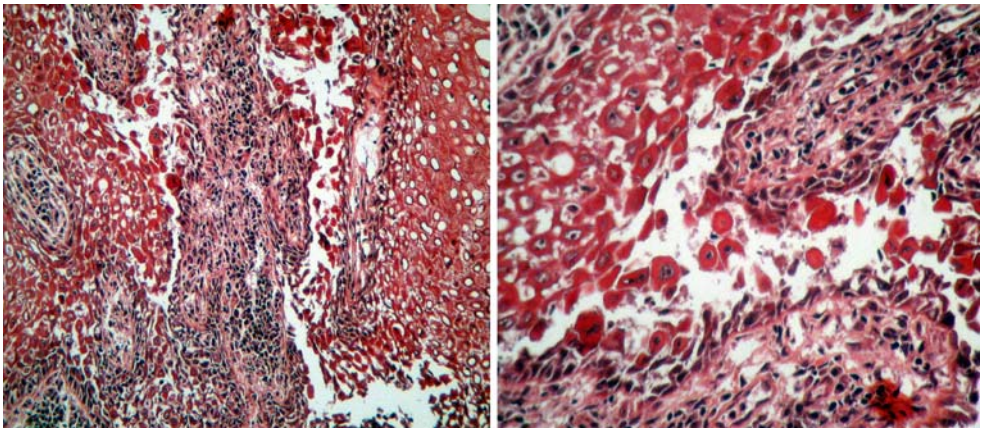

Fig. 2 Biopsy of buccal mucosa: intercellular oedema, acantholysis, lymphocyte infiltration→ pemphigus vulgaris (HE 100×)

the B symptoms and paraneoplastic pemphigus vulgaris supported the diagnosis of CD. Thoracic CT and crista biopsy were performed with negative results. Considering her young age non-cytostatic immunomodulatory therapy was begun. She was treated on a daily basis with 32 mg methylprednisolone, 200 mg thalidomide and 150 mg cyclosporin-A. She had no clinical symptoms, her albumin and CRP levels were normal, but the IL-6 level was elevated (12.4 pg/ml). The control abdominal ultrasonography and CT showed a small residual tumour (50×40 mm) on the bladder in September 2005. Repeated surgery had to be done to remove the residual tumour in January 2006. At that time, the histological examination showed a transient type between plasma cell and vascular variant. After the operation, the steroid dose was decreased to 8 mg daily, together with the initial dose of thalidomide and cyclosporin-A. Because she developed hypertension her cyclosporin-A dose had to be reduced to 100 mg daily 1 month later, and 2.5 mg ramipril was started. Cyclosporin-A serum levels were monitored continuously. The reconstruction of the tongue and removal of pyogen granulomas in the mouth were performed in April 2006 (Figs. 5, 6). ^{18}FDG PET/CT examination showed a 36×23 mm low metabolic active mass (SUV max: 3,3) in the right iliacal region (Fig. 7) in September 2007, but our patient had no symptoms or complaints and her laboratory parameters were normal. At present, almost 4 years after the onset of the disease, she is on 200 mg thalidomide daily and no tumour progression can be seen.

Discussion

The etiology and pathogenesis of CD are not completely understood. Different cytokines can play a role in the pathogenesis of the disease. Abnormally high levels of cytokines (IL-6, IL-10) have been reported in patients with multicentric CD (MCD) and have been implicated in the pathogenesis of MCD, especially in HIV-infected patients [3, 4]. IL-6 is a 22–30 kDa glycoprotein, which is produced

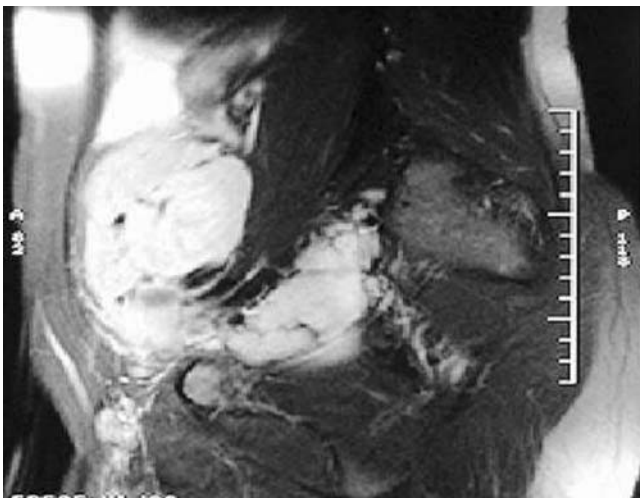

Fig. 3 Pelvic MRI (the *arrow* indicates the 15×6×5 cm tumour)

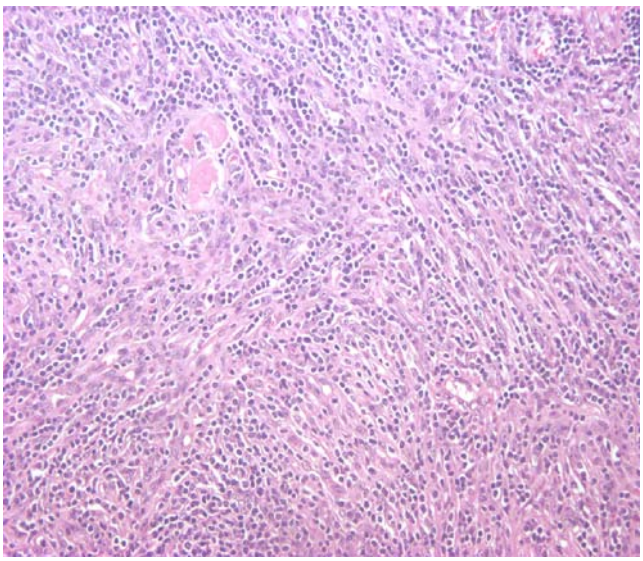

Fig. 4 Lymphocytic infiltration and vascular proliferation: hyaline-hypervascular Castleman's disease (HE 100×)

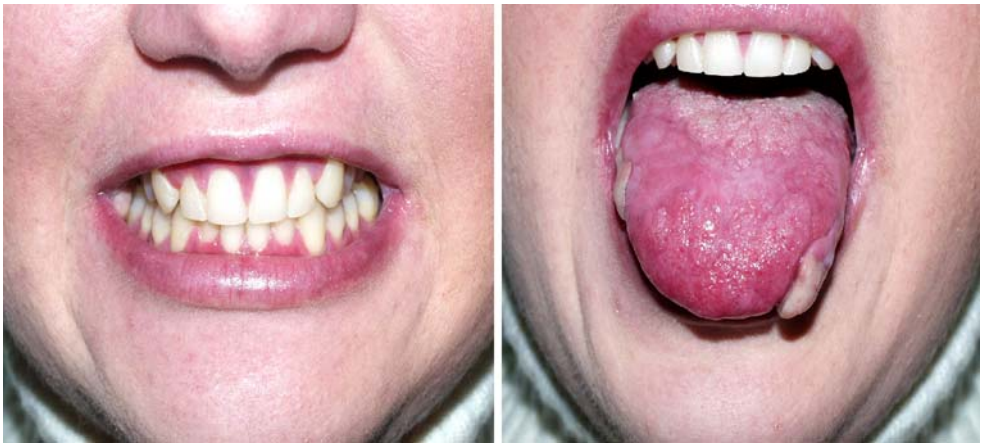

Fig. 5 Before tongue reconstruction

by mononuclear phagocytes, endothelial cells, fibroblasts and activated T cells. It affects B cells, thrombocytes, macrophages, T-cells, thymocytes, endothelial cells and hepatocytes. It induces the production of acute phase proteins, and helps the differentiation of T- and B-cells [5]. Henceforward it activates haemopoetic progenitor cells, and goes on as a growth factor of myeloma and plazmocytoma cells. Several different mechanisms have been proposed to stimulate IL-6 production. Dysregulation of IL-6 production or the cell-signalling pathway downstream of the IL-6 receptor have been hypothesized to play a role in a number of pathological conditions and may explain the endogenous production of this human cytokine [3]. In the multicentric plasma cell type, IL-6 production may be viral-encoded. Recently, infection with HHV-8 has been proposed as a possible etiologic agent. HHV-8 is known to encode a viral-IL6 (v-IL6), with approximately 50% similarity to the human IL-6 (hIL-6) gene at the amino acid level. Human IL-6 binds to forms a bond with the gp130 cellular receptor and activates the Janus kinase/signal transducers and activators of transcription (Jak/Stat) cell signalling pathway through the formation of a heterodimer with IL-6 binding protein, IL-6Rα. Viral IL-6 may also bind to IL-6Rα and the complex with gp130 can activate the downstream Jak/Stat pathway [3]. Exacerbations of MCD in HIV-infected patients are associated with high levels of IL-6, IL-10 and a high viral load for HHV-8 [4]. The development of non-Hodgkin's lymphoma (NHL) in MCD may also be attributed to the presence of HHV-8. Two rare types of NHL, primary effusion lymphoma and plasmablastic lymphoma, are clearly related to HHV-8. In the latest updated Lymphoma Classification of 2008 by the WHO, there is new category known as large B-cell lymphoma arising in HHV-8-associated multicentric Castleman disease [6]. Unknown stimulus is responsible for the cases of HHV-8 negative MCD. In conclusion, the recent findings of cytogenetic changes in stromal cells of the hyaline vascular type and the role of IL-6 and HHV-8 in the pathogenesis of the plasma cell type suggest that hyaline vascular and plasma cell Castleman's disease should be regarded as separate diseases. Our patient had no HHV-8 infection.

The expression of vIL-6 may also link the proliferation of plasma cells and vessels seen in CD, as vascular endothelial growth factor (VEGF) levels in the supernatant of vIL-6 expressing cells have been shown to be several times higher than those of (= VEGF levels) the same cells without the expression of vIL-6. Viral IL-6 was expressed in both HIV-positive, and HIV-negative CD patients' lymph nodes. IL-6 was detected in the germinal center of lymph nodes in plasma cell type UCD and MCD alike. All the symptoms and laboratory abnormalities were resolved via the surgical resection of the node, which coincided with declines in serum IL-6 levels [3, 4].

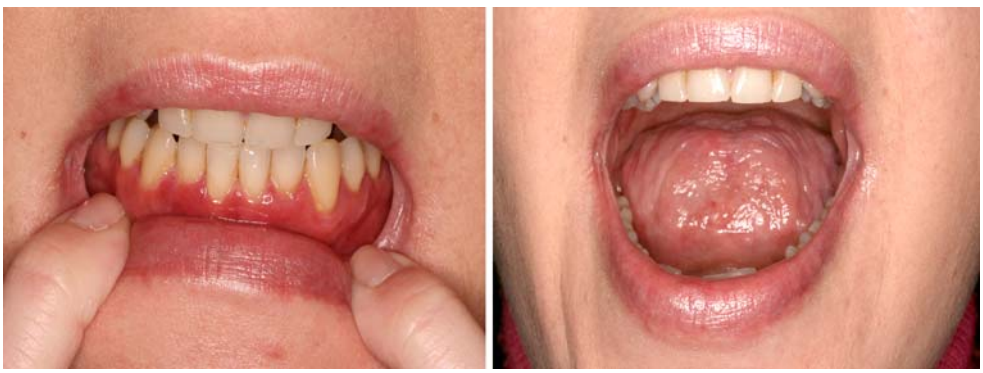

Fig. 6 After the operation (2007 March)

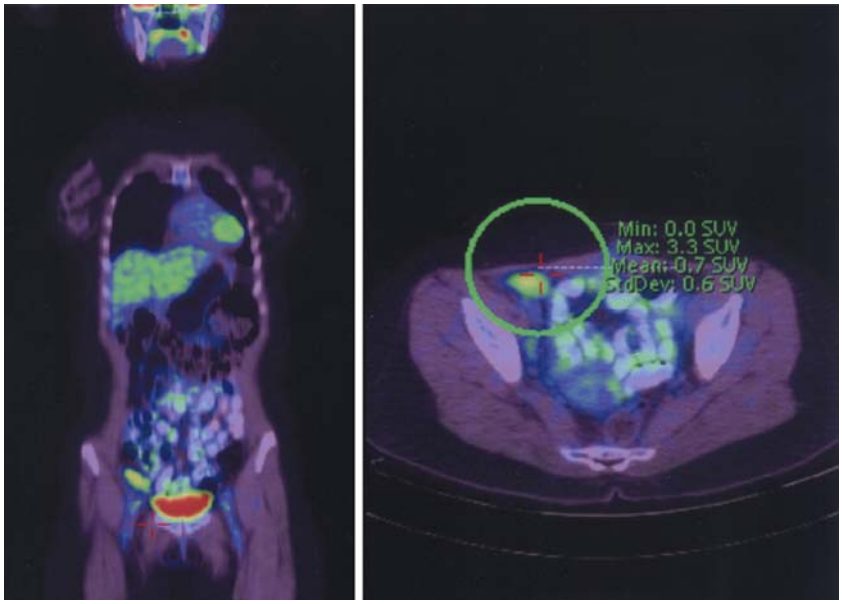

Fig. 7 18-FDG whole-body PET/CT: 36×23 mm low metabolic active mass (SUV max: 3,3)in the right iliacal region

VEGF stimulates the growth of endothelial cells and is capable of controlling blood vessel formation. The VEGF level was elevated in the lymph nodes and the serum according to a study [3] in which the HHV-8 infection status was not examined. VEGF may play a role in the pathophysiology of CD, but it seems unlikely to account for all the pathological and clinical manifestations of the disease [3].

According to some publications, the initial step in the development of CD appears to be the production of IL-6 by B cells in the mantle zone of lymph nodes, which, in the majority of cases, is stimulated by HHV-8 infection and, in a minority of them, by a heretofore unidentified exogenous or endogenous factor. The local elaboration of IL-6, and in turn VEGF, produces the characteristic B-cell proliferation and vascularization in CD. In patients with MCD, systemic symptoms may result from the circulation of IL-6 or IL-6-producing B cells, the generation of excess antibodies or disseminated HHV-8 infection [3].

MCD can be associated with autoimmune diseases. Paraneoplastic pemhigus (PNP) is frequently associated with CD. PNP is an autoimmune syndrome that was first described by Anhalt et al in 1990 [7].

The newly proposed diagnostic criteria (that are uniform in all patients) are as follows [8]:

- intractable stomatitis,
- polymorphic cutaneous lesions that show histological features of acantholysis, lichenoid or interface dermatitis,
- presence of autoantibodies against high molecular weight keratinocyte proteins, including desmoplakins,
- association with specific groups of lymphoproliferative diseases and
- progressive disease that is refractory to treatment, with a fatal outcome in most cases.

PNP with CD can cause serious complications (bronchiolitis obliterans, respiratory failure), that can be treated with combined immunomodulatory therapy after surgery. Our patient had four of these criteria, but the clinical course was more benign. Her disease responded to non-cytostatic immunomodulatory therapy, and she had no respiratory complications.

At present, there is no standard therapy for CD, because it's rarity and heterogeneity.

We have more therapeutic options depend on form of disease.

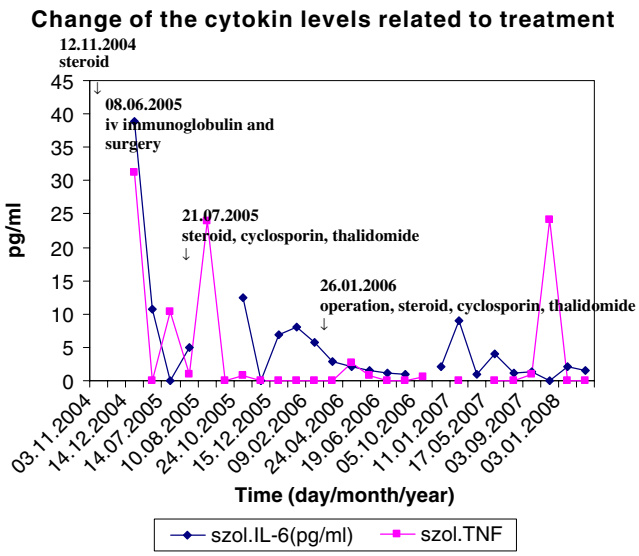

Fig. 8 Change of the cytokin levels related to treatment

a. surgery

Surgery should be curative for localized Castleman disease. Clinical abnormalities may disappear after the excision of the affected lymph nodes in patients with localized Castleman disease [3]. Occasionally, in multicentric Castleman disease, the surgical removal of involved lymph nodes may cause improvement in symptoms, probably related to a "debulking" effect, but any improvement is usually transient [9]

b. irradiation

If surgical resection isn't possible, irradiation is an effective alternative, with response rates up to 72% [9].

c. a, and b, combination
d. non-cytostatic immunomodulatory therapy

Steroids have been used to control inflammation, which has lympholytic effect, but remission is observed in only a small proportion of the patients treated with steroids alone. Lasting remissions are rare, increasing the risk of infections. The use of steroids is suggested when definitive therapy has not been decided or will be delayed [9]. Chorzelski et al treated a young male patient with PNP associated Castleman disease, myasthenia gravis and bronchiolitis obliterans. He got steroid, cyclophosphamid, intravenous immune globulin, cyclosporine A and plasmapheresis was [10]. There is no consensus as to which immunosuppressive regimen is most effective in Castleman's disease with PNP.

e. chemotherapy

Chemotherapy will be the first option chosen in most symptomatic patients. It is ranging from the use of single agents (chlorambucil, cyclophosphamid, vinblastin, etoposid, interferon) to multidrug combinations (CVP or CHOP).

f. anti-CD20 therapy (e.g. rituximab)

Rituximab has been effective in both HIV-positive and negative patients. It seems promising treatment. It could enhance the activity of chemotherapy, as in NHL.

g. antiviral therapy

Ganciclovir has reportedly been successful in reducing the frequency of clinical flares and detectable HHV-8 DNA. Symptoms of MCD burned up in some patients, when used of HAART (highly active antiretroviral therapy), so it's role problematic [9].

h. tocilizumab (anti-IL-6 receptor antibody)

There are some data of successful treatment with monoclonal IL-6 antibody and humanized anti-IL-6 receptor antibody MCD [3, 11]. Steroid dose was decreased or it's use was discontinued in some patients, who got tocilizumab. Some patients received this therapy for up to 3 years, and side effects were not heavy [9].

i. other (bortezomib, thalidomide)

Thalidomide, a disruptor of the IL-6 pathway, has controlled the symptoms and corrected most of the laboratory abnormalities (Fig. 8) [12, 13]. Nikolskaia et al have reported some benefits of using combined treatment with prednisone, cyclosporin-A and rituximab. He successfully treated a patient (who had PNP with CD) with cyclosporin-A, thalidomide and prednisone. After 24 months the patient had no recurrence of the tumour [14]. There are no data about how long thalidomide must be used. Cunha et al used thalidomide in a woman with PNP, and it was effective, but once the treatment with thalidomide had been discontinued, severe lesions returned [15]. Bortezomib is a proteosome inhibitor that interacts negatively with autocrine IL-6 production. Hess et al. reported successful treatment with bortezomib in a patient with MCD [16].

In addition to the difficulties to choose an effective therapy, the lack of a standardized method to monitor MCD presents another obstacle in the management of the disease. HHV-8 viremia, inflammatory markers, cytokin levels (IL-6, TNF-α) and ^{18}FDG-PET/CT could all help to monitor MCD and define remission and relapse [17] according to the laboratory parameters of the patient(s) in the study.

We used cyclosporine-A, steroid and thalidomide successfully to treat our patient. Chemotherapy would not have been a good choice, because she was young, in fertile age. Our patient had a mixed-type of the disease, i.e. pelvic CD with PNP, which makes her case quite / very / especially interesting, since there are only few cases of pelvic CD in the literature [18]. The prognosis of this patient is unpredictable. She is given non-cytostatic immunomodulatory therapy, but we do not know how long she should / will have to undergo treatment. The PNP is well controlled, but ^{18}FDG PET/CT has shown an active mass with low metabolism in the right iliac region (SUV max: 3.3), while the level of IL-6 has been found normal. Our patient's quality of life is the same as that of the normal population.

References

1. Castleman B, Thowne VW (1954) Case records of the Massachuetts General Hospital weekly clinicopathological exercises: Case 40011. N Eng J Med 250:26–30
2. van den Berge M, Pauwels P, Jakimowicz JJ et al (2002) Hyaline vascular Castleman's disease: a case report and brief review of the literature. Neth J Med 60(11):444–447, Dec
3. Casper C (2005) The aetiology and management of Castleman disease at 50 years: translating pathophysiology to patient care. Br J Haematol 129:3–17

4. Oksenhendler E, Carcelain G, Aoki Y et al (2000) High levels of human herpesvirus 8 viral load, human interleukin-6, interleukin-10, and C reactive protein correlate with exacerbation of multicentric Castleman disease in HIV-infected patients. Blood 96:2069–2073
5. Waterston A, Bower M (2004) Fifty years of multicentric Castleman's disease. Acta Oncologica 43:698–704
6. Harris NL, Swerdlow S, Campo E et al (2008) The World Health Organization (WHO) classification of lymphoid neoplasms: what's new? Ann Oncol 19(4):119
7. Anhalt GJ, Kim SC, Stanley JR et al (1990) Paraneoplastic pemphigus. An autoimmune mucocutaneus disease associated with neoplasia. N Engl J Med 323:1729–1735
8. Anhalt GJ (2004) Paraneoplastic pemphigus. J Investig Dermatol Symp Proc 9(1):29–33
9. Dham A, Peterson BA (2007) Castleman disease. Curr Opin Hematol 14:354–359
10. Chorzelski T, Hashimoto T, Maciejewska B et al (1999) Paraneoplastic pemphigus associated with Castleman tumor, myasthenia gravis, and bronchiolitis obliterans. J Am Acad Dermatol 41 (3):3939–3400
11. Nishimoto N, Kanakura Y, Aozasa K et al (2005) Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. Blood 106:2627–2632
12. Starkey C, Joste N, Lee FC (2006) Near-total resolution of multicentric Castleman disease by prolonged treatment with thalidomid. Am J Haematol 81:303–304 (letter)
13. Lee FC, Merchant SH (2003) Alleviation of systemic manifestations of multicentric Castleman's disease by thalidomide. Am J Hematol 73:48–53
14. Nikolskaia OV, Nousari CH, Anhalt GJ (2003) Paraneoplastic pemphigus in association with Castleman's disease. Br J Dermatol 149:1143–1151
15. Cunha PR, de Oliveira JR, Salles MJ et al (2004) Pemphigus vulgaris with involvement of the cervix treated using thalidomide therapy. Int J Dermatol 43(9):682–684
16. Hess G, Wagner V, Kreft A et al (2006) Effects of bortezomib on pro-inflammatory cytokine levels and transfusion dependency in a patient with multicentric Castleman disease. Brit J Haematol 134:544–549
17. Diéval C, Bonnet F, Mauclére S et al (2007) Multicentric Castleman disease: Use of HHV8 viral load monitoring and positron emission tomography during follow-up. Leuk Lymphoma 48(9):1881–1883
18. Nakamura Y, Tokuyama O, Muso A et al (2002) Asymptomatic pelvic Castleman disease in an infertile woman: case report. Arch Gynecol Obstet 269:156–158