ABSTRACT

We describe a 27-year-old female with a mesenterial localisation of the hyaline vascular type of Castleman’s disease. A review of the literature is given with emphasis on the different pathogenesis of the subtypes. The hyaline vascular type is a disorder of stromal cells, which can be complicated by the development of soft tissue sarcomas. The plasma cell type is a plasma cell disorder with elevated levels of interleukin-6 (IL-6). In the multicentric type, infection with human herpes virus-8 (HHV-8) plays an important role in the pathogenesis. The development of Kaposi’s sarcoma and some lymphomas are related to the presence of HHV-8. As the different subtypes have a different pathogenesis they should be regarded as distinct diseases.

INTRODUCTION

In 1956 Castleman et al. described a new disease entity of localised mediastinal lymph node hyperplasia, now referred as Castleman’s disease.1 Subsequent reports described additional sites of disease and different names were used for this entity, including angiofollicular or giant lymph node hyperplasia. In 1969 Flendrig et al.2 and later Keller et al.3 recognised a different histological type, which is now referred to as the ‘plasma cell’ type in contrast to the ‘hyaline vascular’ type described by Castleman et al. Both groups proposed that these two types were manifestations of the same disease because there were cases with overlapping histological features. A systemic lymphoproliferative disorder with morphological features of the plasma cell type is subsequently described as multicentric Castleman’s disease.4

We describe a patient with hyaline vascular Castleman’s disease and give a review of the literature with a special focus on the pathogenesis of this rare disease.

CASE REPORT

A 27-year-old female presented with intermittent pain in the upper abdomen, which was not continuous. She complained of nausea and heartburn. She had lost 2.5 kg after following a diet and had not experienced any fever or night sweats. Her previous medical history was uneventful. She was not taking any medication. Physical examination revealed a healthy looking woman with a normal blood pressure and pulse rate. There were no enlarged lymph nodes. Examination of the heart and lungs was normal. In the upper abdomen there was a palpable mass of 3 cm, which was mobile. Rectal and vaginal examination was normal. Laboratory results revealed no abnormalities. A CT scan of the abdomen showed a tumour of 3 x 4.5 cm near the stomach (figure 1). An ultrasound-guided biopsy was inconclusive, so an incisional biopsy of the mass was performed. Pathological examination showed Castleman’s disease of the hyaline vascular type. The lesion was completely resected. Two years later the patient is well without any evidence of recurrent disease.

PATHOLOGY

A tumour of 3 cm was received consisting of lymph node tissue, with follicles that possessed a broad mantle zone
surrounding relatively small germinal centres. The germinal centres were predominated by follicular dendritic cells, which were mixed with small numbers of follicle centre cells. These germinal centres were penetrated by hyalinised venules. The follicles were separated by hypervascular interfollicular tissue. These findings are consistent with a diagnosis of hyaline vascular Castleman’s disease (figure 2).

The germinal centres were predominated by follicular dendritic cells, which were mixed with small numbers of follicle centre cells. These germinal centres were penetrated by hyalinised venules. The follicles were separated by hypervascular interfollicular tissue. These findings are consistent with a diagnosis of hyaline vascular Castleman’s disease (figure 2).

discussion

The patient presented here suffered from Castleman’s disease of the hyaline vascular type. Castleman’s disease is a heterogeneous disorder with overlapping clinical features and histological variants. Traditionally three histological variants (hyaline vascular, plasma cell and mixed) and two clinical types (localised and multicentric) can be distinguished. However, the majority of cases can be categorised as localised hyaline vascular, localised plasma cell or multicentric plasma cell (table 1).

The localised hyaline vascular type is seen in 90% of the cases of localised disease.\(^5\) It is often asymptomatic or, as in our patient, there are symptoms caused by the mass effect of the lesion. The diagnosis is made on the histological appearance of the lymph node, which shows small hyaline vascular follicles with interfollicular capillary proliferation. The localised plasma cell type is seen in the other 10% of the cases of localised disease. Often patients present with constitutional symptoms such as fever, fatigue and weight loss and also laboratory abnormalities. Histology of the affected lymph nodes shows large follicles with intervening sheets of plasma cells. In both histological variants the treatment is surgical resection. If surgery is not possible, radiotherapy can be successful.\(^6\) The prognosis of localised Castleman’s disease is good.

The multicentric type is a systemic disease with disseminated lymphadenopathy, hepatosplenomegaly and constitutional symptoms. Histologically, it is similar to the localised plasma cell type. It can be associated with autoimmune diseases. When polyneuropathy is present the distinction between the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) and Castleman’s disease can be difficult. The course of multicentric Castleman’s disease is unpredictable. It can be stable or can be characterised by remissions and exacerbations, while in other patients it has a fatal course within a few months. The main causes of mortality are infections and malignancies, especially lymphomas and Kaposi’s sarcoma.\(^7\) Some patients respond to steroids, but they often relapse after the steroids are tapered. Chemotherapy regimes as used in the treatment of aggressive lymphoma give a sustained response in 30 to 40%.\(^8\) However, the risk of infection is high. There are several case reports of alternative approaches after the failure of conventional chemotherapy such as treatment with high-dose melphalan with autologous bone marrow transplantation, anti-IL-6 monoclonal antibody and interferon alpha.\(^9\)\(^-\)!\(^11\)

A subgroup of multicentric Castleman’s disease is described in patients with HIV infection. These patients more often have pulmonary symptoms and there is a stronger association with Kaposi’s sarcoma.\(^12\) The relationship between the hyaline vascular and plasma cell type has been a matter of debate. Based on the existence of mixed cases it has been suggested that the plasma cell variant represents an earlier and the hyaline-vascular variant a later stage of the same process or that their difference is due to a different immune response. Frizzera considered the hyaline vascular type and the plasma cell type as two distinct disease entities.\(^5\) In his opinion there were no mixed cases. The hypothesis that the different histological types are distinct entities is supported by
recent findings regarding the aetiology of the different subtypes.

Several authors have pointed to the important role of follicular dendritic cells (FDCs) in the pathogenesis of hyaline vascular Castleman’s disease (HVCD). Dysplastic changes and proliferation of these cells have been described.13-16 There are several reports of HVCD complicated by follicular dendritic cell sarcoma and vascular neoplasms.17-19 Recently two reports demonstrated a chromosomal abnormality in HVCD pointing to a clonal proliferation of the follicular dendritic cells.20,21 These chromosomal abnormalities may explain why malignancies of stromal cells can arise in this type of Castleman’s disease. In our patient this chromosomal abnormality was not found. Therefore, HVCD can be considered a disorder of stromal cells. Proliferation and neoplastic transformation can result in the development of sarcomas.

In the pathogenesis of the plasma cell type, IL-6 seems to play a central role. High levels of IL-6 have been demonstrated and can explain the systemic manifestations in patients with this type of Castleman’s disease. In our patient this chromosomal abnormality was not found. Therefore, HVCD can be considered a disorder of stromal cells. Proliferation and neoplastic transformation can result in the development of sarcomas. In the pathogenesis of the plasma cell type, IL-6 seems to play a central role. High levels of IL-6 have been demonstrated and can explain the systemic manifestations in patients with this type of Castleman’s disease.8,14,15 Blocking of the IL-6 signal transduction by anti-IL-6 receptor antibody therapy can alleviate the systemic manifestations.9 In the hyaline vascular type there is no IL-6 expression.15

In the localised plasma cell type surgical resection of the hyperplastic lymph nodes results in complete resolution of constitutional symptoms and laboratory abnormalities. This can be explained by the finding of high IL-6 production by the hyperplastic lymph node itself.16 In the multicentric plasma cell type, IL-6 production may be viral-encoded. Human herpes virus-8 (HHV-8) could be detected in all patients with multicentric Castleman’s disease and human immunodeficiency virus (HIV) and also in 7 of 17 cases of HIV-negative patients.16 HHV-8 is known to encode a viral-IL6 (v-IL6), which can induce production of endogenous human IL-6.17 Exacerbations of multicentric Castleman’s disease in HIV-infected patients are correlated with high levels of IL-6, IL-10 and a high viral load for HHV-8.18 HHV-8 is also known as Kaposi’s sarcoma-associated herpes virus and this can explain the association between multicentric Castleman’s disease and Kaposi’s sarcoma. The development of non-Hodgkin’s lymphoma (NHL) in multicentric Castleman’s disease may also be attributed to the presence of HHV-8.19 Two rare types of NHL are clearly related to HHV-8: primary effusion lymphoma and plasmablastic lymphoma.20 Therefore HHV-8 seems to play an important role in the pathogenesis of multicentric Castleman’s disease, especially in patients with HIV.

It can be hypothesised that patients with multicentric Castleman’s disease without evidence of an infection with HHV-8 have in fact another disorder, as similar histopathological features can be observed in autoimmune disorders, primary immunodeficiencies and in association with skin diseases and membranous nephropathy.8,9 Another possibility is that a yet unknown stimulus is responsible for the cases of HHV-8 negative multicentric Castleman’s disease.

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.
REFERENCES