Case Presentation 12
Multicentric Castleman's Disease, Mixed Type

Case Report
The patient is a 51-year-old Asian female who presents to the University of California, Davis Dermatology Clinic with a six-year history of a progressive rash involving the scalp, face, trunk, and arms. She reported that the rash first started in her right antecubital fossa as a small pink macule that gradually enlarged over time. The lesions followed an evolutionary course, developing hyperpigmentation with thinning centrally. She developed more lesions involving the face and trunk. Various biopsies were procured over a period of a few years which were suggestive of an evolving low-grade lymphoproliferative disorder although without diagnostic features of lymphoma. The patient had a subsequent systemic work up which was remarkable for lymphadenopathy with a lymph node biopsy demonstrating reactive plasmacytosis. Clinical examination revealed many well demarcated hyperpigmented red-brown atrophic plaques on the face, trunk, and bilateral upper arms (figure 1,2). The patient’s serologic studies were remarkable for a polyclonal hypergammaglobulinemia although there was no evidence of a monoclonal paraproteinemia. The patient has continued to develop new lesions and remains refractory to topical steroids and other therapies. The dermatologist elected to do some of the systemic in nature. Her current medications include vinegar tablets, calcium, and stress B complex.

Light Microscopy
A skin biopsy showed a nodular pattern of lymphocytic infiltration involving the superficial and deep dermis (figure 3). In particular, there were well defined germinal centers surrounded by cuffs of small lymphocytes (figure 4). Interposed perivascular collections of mature plasma cells were noted (figure 5). The germinal centers had a varied quality, ranging from hyperplastic to atrophic (figure 6). Many of the germinal centers contained thick hyaline-like vessels which assumed a perpendicular orientation to the long axis of the germinal center (figure 6). The vascular quality of the germinal centers was apparent in both atrophic as well as more activated appearing germinal centers (figure 7).

Phenotypic Studies
The germinal centers showed a reactive phenotype. They expressed Bcl-6 and CD10 while the centrocytes and centroblasts did not display any positivity for Bcl-2 (figure 8). There was a well defined dendritic cell network cell compartment with the CD68+ macrophages (figure 9). In many cases, there was evidence of light chain restriction for lambda, finding similar to her previous biopsies. Despite the presence of lambda light chain restriction, the plasma cells assumed a perivascular disposition within the biopsy without an effacing tumefactive growth pattern and as well there was no evidence of atopia amidst the clonally restricted plasma cell population (figure 9, figure 10).

Discussion
The patient presents with very classic clinical and histologic findings of multicentric Castleman's disease. The brownish-red plaques are a cardinal feature of this entity clinically and demonstrates a striking resemblance to cutaneous and or systemic plasmacytosis as will be discussed presently. Light microscopically the case showed features of so-called mixed Castleman’s disease of both the hyaline vascular and plasma cell variants respectively. The vascularity of the germinal centers with concomitant atrophy of the germinal center are among the typical features that one encounters in hyaline vascular Castleman's disease. The morphologic clue indicative of the plasma cell variant of Castleman's disease was in the context of lambda light restricted plasma cells. In the plasma cell variant of Castleman's disease at least in the inception of the disease – the plasma cells are characteristically polytypic although light chain restriction most commonly for lambda emerges in a number of the cases. A significant portion of patients who have isolated restriction in the lambda chain plasma cell variant of multicentric Castleman's disease will subsequently develop post germinal center lymphomas including marginal zone lymphoma, Waldenstrom's macroglobulinemia and Richter syndrome. Hyaline vascular Castleman's disease is a relatively aggressive lymphoproliferative disorder that is most commonly treated with systemic agents. It has been linked with human herpes type 8 (HHV-8) infection which is an oncogenic virus although not all cases of multicentric Castleman's disease are associated with HHV-8 infection. The most common setting in North America in which multicentric Castleman's disease develops is in the context of immunocompromised patients with human immunodeficiency virus infection (HIV). Castleman's disease has been associated with certain autoimmune disorders including myasthenia gravis, Evans syndrome, x-linked celiac disease, Graves' disease, and ulcerative colitis. Castleman's disease was first described by Benjamin Castleman in 1966 (Keller et al 1972). Multicentric Castleman's disease has been observed in association with Kaposi's sarcoma and POEMS syndrome (peripheral polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin signs) (Luppi M et al 1996; Mesri et al, 1996; Ceasarman and Knowles, 1996).
There is significant cytokine dysregulation implicated in multicentric Castleman's disease involving interleukin 1, tumor necrosis factor alpha, and interleukin 6.

Sorologic studies show high interleukin 6 levels and as well HHV-8 DNA can be detected in the serum in cases of multicentric Castleman’s disease associated with HIV infection. It has been postulated that the initial trigger could be HHV-8 infection associated with abnormal interleukin-6 production. It is well known that the IL-6 pathway is important in driving HHV-8 infected naïve B cells to differentiate into plasmablasts. At the same time HHV-8 encodes a viral IL-6 which has many of the physiologic features of human IL-6 (Neipel et al 1996). Hence, there is a very interesting interplay between HHV-8 infected B cells under the influence of viral IL-6 to undergo differentiation into plasma cells and subsequent oncogenic transformation, eventuating into a high grade lymphoma. Therapy directed at eradicating the virus implicated in multicentric Castleman's disease has been suggested although does not define the basis of treatment. Instead therapy has addressed the B cell lymphoproliferative aspects of the disease as well utilizing inhibitor agents that attenuate the dysregulated cytokine cascade. Biologic therapy targeting the various interleukins implicated in multicentric Castleman's disease, most notably IL-6, is another potential avenue of therapeutic intervention.

The pathologic findings in Castleman’s disease reflect the sequence of the various cytokines that drive this lymphoproliferative process, specifically and most importantly interleukin 6. Interleukin 6 induces vascular proliferations in the lymph nodes and skin (Nishi and Yarumama 2000). As well as vascular proliferations in the lymph nodes and skin (Nishi and Yarumama 2000). Interleukin 6 has a direct effect of promoting plasma cell differentiation. Castleman's disease is a lymphoproliferative disorder of unknown etiology characterized by enlarged hyperplastic lymph nodes with marked vascular proliferation.

The VEGF levels of the sera and the supernatants of the cultured lymph nodes were higher in patients with Castleman’s disease compared to normal controls. VEGF is strongly expressed in plasma cells in the interfollicular region of the lymph nodes, but rarely in normal lymph nodes. The dysregulated IL-6 gene expression including a viral homologue of IL-6 (vIL-6) encoded by KSHV/HHV-8 has been shown to induce VEGF expression in a paracrine mechanism whereby plasma cells are the source of VEGF production, VEGF then induces vascular proliferations in the lymph nodes and skin (Nishi and Yarumama 2000). The fibroplasia that is noted to varying degrees may reflect the role of plasma cells of the IgG4 subset.

The epidemiology of Castleman's disease is different in Western countries compared to Castleman's disease in Asia. In Western countries, multicentric Castleman's disease is strongly linked to human immunodeficiency virus (HIV) disease and HHV-8 infection while in Japanese there is no significant association with HIV although one must postulate a common trigger in non-human immunodeficiency virus associated Castleman's disease. In this idiopathic form of Castleman's disease, a specific role for HHV-8 infection has not been documented although other viruses may be implicated. It has been suggested that there are two variants of HHV-8 mixed multicentric Castleman's disease in Asia , namely idiopathic plasmacytic lymphadenopathy (IPL) with polyonal hypergammaglobulinemia and a non-idiopathic variant unaccompanied by polyonal lymphadenopathy. The non-idiopathic variant is also referred to as TAFRO syndrome or non-IPL. Among the symptoms are thrombocytopenia, anasarca, fever, reticulin fibrosis simulating myelofibrosis, and organomegaly without hyper-globulinemia. A hyaline vascular histology is seen; there is no association with HHV-8 infection.
The variant of multicentric Castleman’s disease designated as idiopathic polyclonal lymphadenopathy with polyclonal hypergammaglobulinemia resembles the plasma cell variant of multicentric Castleman’s disease in Western countries although in the absence of HHV-8 or HIV infection. This patient appears to have features of idiopathic mixed multicentric Castleman’s disease as opposed to the non-idiopathic variant (i.e., TAFRO syndrome). In some ways the designation of idiopathic versus non-idiopathic appears confusing since neither variant of endemic multicentric Castleman’s disease is attributable to HHV8 infection (Kawabata et al 2013).

The differential diagnosis in this case is with systemic plasmacytosis. There are many overlapping features of so-called systemic plasmacytosis with the idiopathic variant of multicentric Castleman’s disease including the distinctive brown red appearance of the lesions along with their site localization and accompanying lab abnormalities including a significant polyclonal hypergammaglobulinemia. Cutaneous and systemic plasmacytosis has a predilection to involve people of Asian extraction from Asia and hence is similar to the higher frequency of non-HIV associated multicentric Castleman’s disease among Asians. Environmental and genetic factors are clearly a factor and likely both conditions are pathogenetically related. In both multicentric Castleman’s disease and cutaneous plasmacytosis, there may be a role for the rare subset of IgG4 positive staining plasma cells based on the extent of infiltration of biopsy samples with IgG4 positive staining plasma cells in both of these closely related conditions (Haque et al 2011; Honda et al, 2013). Lymphadenopathy is frequently observed in patients with immunoglobulin G-related disease (IgG4-RD) and sometimes appears as the first manifestation of the disease. The diagnosis of IgG4-related lymphadenopathy is complicated owing to a great historical diversity, with at least 5 histological subtypes. Indeed, lymph node biopsy may be performed under the suspicion that the lymphadenopathy is a malignant lymphoma or other lymphoproliferative disorder. The diagnosis of IgG4-RD is characterized by both elevated serum IgG (>150 mg/dL) and histopathological features, including a dense lymphoplasmacytic infiltrate rich in IgG4(+) plasma cells (IgG4+/IgG+ plasma cell ratio >40%). Patients with hyper-interleukin (IL)-6 syndromes such as multicentric Castleman’s disease and rheumatoid arthritis often fulfill the diagnostic criteria for IgG4-RD. Owing to these factors, IgG4-RD cannot be differentiated from hyper-IL-6 syndromes on the basis of histological findings alone. Laboratory analyses are crucial to differentiate hyper-IL-6 syndromes on the basis of histological findings alone. Laboratory analyses are crucial to differentiate between the 2 diseases. Hyper-IL-6 syndromes are characterized by elevated serum levels of IgG, IgM, and C-reactive protein, thrombocytosis, anemia, hypoalbuminemia and hypocholesterolemia. IgG4 related disease does not exhibit these aforesaid abnormalities (Sato Y, Yoshino T 2012).

Figure Legend

Figure 1. The patient presents with multiple dark bronzy red plaques on the back.

Figure 2. As well other germinal centers appear atrophic with a diminished number of centrocytes and centroblasts; the germinal center is identified.

Figure 3. The biopsy shows a superficial and deep nodular lymphocytic infiltrate.

Figure 4. The nodular lymphocytic foci are characterized by well formed germinal centers surrounded by cuffs of small lymphocytes. The nodular lymphocytic foci are confirmed by virtue of staining for the germinal center cell markers Bcl2 and CD10. Illustrated is Bcl6.

Figure 5. Collections of plasma cells are noted in the dermis adjacent to the germinal center-like foci.

Figure 6. Case References


For more information, consultation, or patient referral please contact: