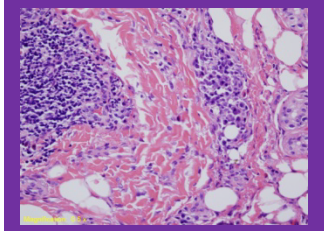
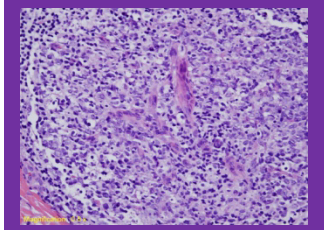
Case Presentation 12

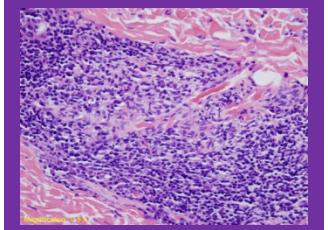
Multicentric Castleman's Disease, Mixed Type

Case author: Cynthia M. Magro, MD **Contributing authors:** Aparche Yang, MD - University of California, Irvine

Dermatopathology
Weill Cornell Medical College







This educational series for physicians is presented by the Weill Cornell Comprehensive Dermatopathology Service

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 remembered that the rash first started in her right antecubetal 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 although none of the treatments administered to date have been 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 highlighted by CD21 and CD23. In examining the plasma cells there was evidence of light chain restriction for lambda, a 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 atypia amidst the clonally restricted plasma cell populace (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 percentage of patients who have clonal restriction in the setting of plasma cell variant of multicentric Castleman's disease will subsequently develop post germinal center lymphomas including marginal zone lymphoma, Waldenstrom's macroglobulinemia and multiple myeloma. Multicentric 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, vitiligo, celiac disease, Graves' disease, and ulcerative colitis. Castleman's disease was first described by Benjamin Castleman in 1966(Kller 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.

Serologic 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 plasmablasts with subsequent oncogenic transformation, eventuating into a high grade lymphoma. Therapy directed at eradicating the virus implicated in multicentric Castelman'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 two main histopathologic subtypes of Castleman's disease are the hyaline vascular and plasma cell variants. An intermediate form exhibiting an overlapping morphology between hyaline vascular and plasma cell variants has also been described. In the hyaline vascular variant of Castleman's disease there are reproducible and distinctive abnormalities in the germinal centers characterized by follicular atrophy with intrafollicular and interfollicular neovascularization. The vessels typically assume a perpendicular orientation to the long axis of the germinal center. In the plasma cell variant, the germinal centers are hyperplastic and there are concomitant interfollicular areas of plasma cell infiltration. It has been suggested by some authors that the hyaline vascular variant is thought to be the incipient expression of the disease while the plasma cell form is a later stage lesion of Castleman's disease. The plasma cell variant and or mixed plasma cell and hyaline vascular histology is characteristically seen in patients presenting with multicentric disease while the hyaline vascular form is most commonly seen in the context of unicentric disease although there are rare cases of so called non-idiopathic multicentric Castleman's disease where the hyaline vascular morphology predominates as will be discussed presently. The commonest site for unicentric Castleman's disease is the thorax.

The pathologic findings in Castleman's disease reflect the sequelae of the various cytokines that drive this lymphoproliferative process, specifically and most importantly interleukin 6. Interleukin 6 leads to upregulation of interleukin 10 which has suppressive propertiesaccounting for the atrophy of germinal centers and generalized immunosuppression. It also promotes vascular endothelial cell growth factor. The vascularity of the germinal centers are likely on the basis of enhanced VEGF. In addition the systemic elaboration of VEGFR induces other vasoformative lesions such as eruptive glomeruloid hemangiomas. 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 dyaregulated 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 via a paracrine mechanism whereby plasma cells are the source of VEGF production and induce 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 HHV8- mixed multicentric Castleman's disease in Asia , namely idiopathic plasmacytic lymphadenopathy (IPL) with polyclonal hypergammaglobulinemia and a non-idiopathic variant unaccompanied by polyclonal 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-γ-globulinemia. A hyaline vascular histology is seen; there is no association with HHV-8 infection.

continued

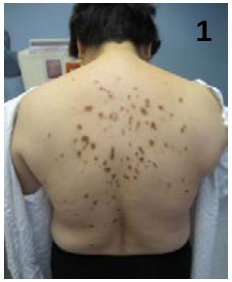
The variant of multicentric Castleman's disease designated as idiopathic polyclonal lymphadenopathy with polyclonal hypergammaglobulinemia resembles the plasma cell variant of multicentric Castleman's disease in Western countries although in the absence of HHV-8 and or HIV infection. This patient appears 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 G4-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 histological 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 IgG4 (>135 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 between the 2 diseases. Hyper-IL-6 syndromes are characterized by elevated serum levels of IgG, IgA, IgM, and C-reactive protein , thrombocytosis, anemia, hypoalbuminemia and hypocholesterolemia. IgG4 related disease does not exhibit these aforesaid abnormalities(Sato Y, Yoshino T 2012).

Case References

1. Keller AR, Hochholzer L, Castleman B. Hyaline-vascular and plasma-cell types of giant lymph node hyperplasia of the mediastinum and other locations. Cancer. 1972 Mar;29(3):670-83.
2. Luppi M, Barozzi P, Maiorana A, Artusi T, Trovato R, Marasca R, Savarino M, Ceccherini-Nelli L, Torelli G. Human herpesvirus-8 DNA sequences in human immunodeficiency virus-negative angioimmunoblastic lymphadenopathy and benign lymphadenopathy with giant germinal center hyperplasia and increased vascularity. Blood. 1996 May 1;87(9):3903-9.
3. Mesri EA, Cesarman E, Arvanitakis L, Rafii S, Moore MA, Posnett DN, Knowles DM, Asch AS. Human herpesvirus-8/Kaposi's sarcoma-associated herpesvirus is a new transmissible virus that infects B cells. J Exp Med. 1996 May 1;183(5):2385-90.
4. Corbellino M, Poirel L, Aubin JT, Paulli M, Magrini U, Bestetti G, Galli M, Parravicini C. The role of human herpesvirus 8 and Epstein-Barr virus in the pathogenesis of giant lymph node hyperplasia (Castleman's disease). Clin Infect Dis. 1996 Jun;22(6):1120-1.
5. Cesarman E, Knowles DM. Kaposi's sarcoma-associated herpesvirus: a lymphotropic human herpesvirus associated with Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman's disease. Semin Diagn Pathol. 1997 Feb;14(1):54-66.
6. Neipel F, Albrecht JC, Ensser A, Huang YQ, Li JJ, Friedman-Kien AE, Fleckenstein B. Human herpesvirus 8 encodes a homolog of interleukin-6. J Virol. 1997 Jan;71(1):839-4
7. Nishi J, Maruyama I. Increased expression of vascular endothelial growth factor (VEGF) in Castleman's disease: proposed pathomechanism of vascular proliferation in the affected lymph node. Leuk Lymphoma. 2000 Jul;38(3-4):387-94.
8. Kawabata H, Takai K, Kojima M, Nakamura N, Aoki S, Nakamura S, Kinoshita T,Masaki Y. Castleman-Kojima disease (TAFRO syndrome) : a novel systemic inflammatory disease characterized by a constellation of symptoms, namely,thrombocytopenia, ascites (anasarca), microcytic anemia, myelofibrosis, renal dysfunction, and organomegaly : a status report and summary of Fukushima (6 June,2012) and Nagoya meetings (22 September, 2012). J Clin Exp Hematop.2013;53(1):57-61.
9. Haque M, Hou JS, Hisamichi K, Tamada K, Cusack CA, Abdelmalek M, Brown RE, Vonderheid EC. Cutaneous and systemic plasmacytosis vs. cutaneous plasmacytic castleman disease: review and speculations about pathogenesis. Clin Lymphoma Myeloma Leuk. 2011 Dec;11(6):453-61.
10. Honda R, Cerroni L, Tanikawa A, Ebihara T, Amagai M, Ishiko A. Cutaneous plasmacytosis: report of 6 cases with or without systemic involvement. J Am Acad Dermatol. 2013 Jun;68(6):978-85.
11. Takeuchi M, Sato Y, Takata K, Kobayashi K, Ohno K, Iwaki N, Orita Y, Yoshino T. Cutaneous multicentric Castleman's disease mimicking IgG4-related disease. Pathol Res Pract. 2012 Dec 15;208(12):746-9.
12. Sato Y, Yoshino T. IgG4-Related Lymphadenopathy. Int J Rheumatol. 2012;2012:572539. doi: 10.1155/2012/572539.

Figure Legend



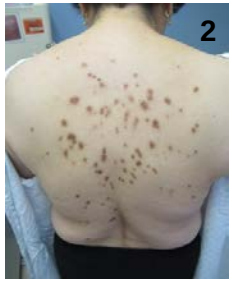


Figure 1, 2: The patient presents with multiple dark bronzy red plaques on the back.

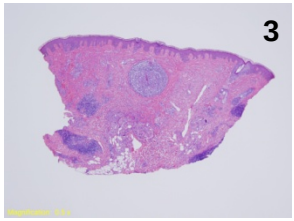


Figure 3: The biopsy shows a superficial and deep nodular lymphocytic infiltrate.

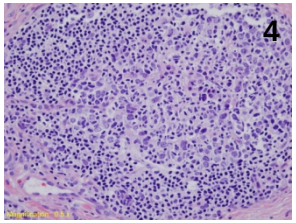


Figure 4: The nodular lymphocytic foci are characterized by well formed germinal centers surrounded by cuffs of small lymphocytes. Note the vascularity of the germinal center although the vessels are not as conspicuous as the vasculature illustrated in figures 6 and 7.

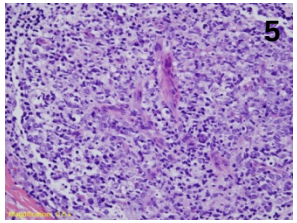


Figure 5: Collections of plasma cells are noted in the dermis adjacent to the germinal center-like foci.

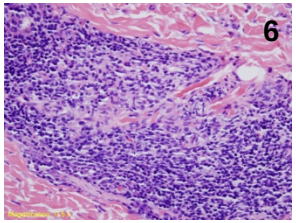
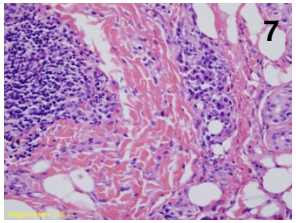


Figure 6: As well other germinal centers appear atrophic with a diminished number of centrocytes and centroblasts; the germinal centers appear hypervascular. The characteristic perpendicular orientation of the vessels to the long axis of the germinal center is identified.



Figures 7: Other germinal centers exhibit both a hyperplastic morphology and also exhibit an aberrant vasculature.

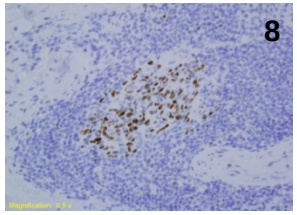


Figure 8: The germinal center nature of the nodular lymphocytic foci are confirmed by virtue of staining for the germinal center cell markers Bcl6 and CD10. Illustrated is Bcl-6.

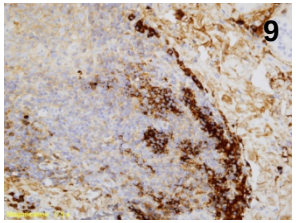


Figure 9: There is evidence of lambda light restriction. Admist the plasma cells.

.

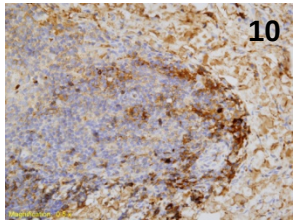


Figure 10: A lesser number of kappa staining plasma cells are identified. Any dominance of lambda over kappa would be indicative of an emerging lambda light chain restricted plasma cell infiltrate indicative of low grade post germinal center B cell lymphoproliferative disease.

Under the direction of Dr. Cynthia M. Magro, the Weill Cornell Comprehensive Dermatopathology Service is a leading edge consultation service and CAP-accredited laboratory for dermatologists, plastic and general surgeons and other dermatopathologists. Dr. Magro is an internationally renowned dermatopathologist, educator and author. She is a Professor of Pathology and Laboratory Medicine at the Weill Cornell Medical College in Manhattan, and is board certified in anatomic pathology, dermatopathology and cytopathology. Dr. Magro is an expert in the diagnosis of complex inflammatory skin diseases. Her areas of expertise include cutaneous manifestations of auto-immune disease, systemic viral disease and vasculitis, atypical drug reactions, benign, atypical and overtly malignant lymphocytic infiltrates of the skin, and diagnostically difficult melanocytic proliferations.The award-winning author of *The Melanocytic Proliferation: A Comprehensive Textbook of Pigmented Lesions*, Dr. Magro has recently completed her second book, *The Cutaneous Lymphoid Proliferation, a comprehensive textbook on benign and malignant lymphocytic infiltrates*. She has co-authored over 280 peer reviewed papers and several textbook chapters. Dr. Magro frequently presents courses on inflammatory skin pathology and difficult melanocytic proliferations to the American Academy of Dermatology, the United States and Canadian Academy of Pathology, and the American Society of Clinical Pathology. Dr Magro has consistently been recognized in Who's Who in America®, Castle Connolly's renowned America's Top Doctors – New York Metro Area® edition and in the Super Doctors® list published in The New York Times Magazine.

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

Cynthia M. Magro, MD,
Director
Weill Cornell Comprehensive Dermatopathology Service
Tel. 212-746-6434
Toll-free 1-800-551-0670
ext. 746- 6434
Fax. 212-746-8570
www.weillcornelldermpath.com