OBSERVATION

Eruptive Cherry Hemangiomatosis Associated With Multicentric Castleman Disease

A Case Report and Diagnostic Clue

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Background: Eruptive cherry hemangiomatosis, which involves the sudden onset of multiple small vascular proliferations, has been rarely reported as a heralding sign of multicentric Castleman disease (MCD) and other lymphoproliferative diseases. We report a case wherein the rapid appearance of cherry hemangiomata is the presenting sign of MCD.

Observations: A 25-year-old man with a 10-year history of benign vascular growths developed 23 cutaneous vascular proliferations and systemic symptoms 5 days prior to presentation. Biopsy of the cutaneous lesions revealed a polypoidal proliferation of vessels consistent with cherry hemangiomata. Laboratory studies disclosed systemic abnormalities, and the findings of a subsequent lymph node biopsy confirmed MCD. Combination chemotherapy was initiated, and the cutaneous proliferations improved in association with the systemic disease.

Conclusions: There is a scarcity of literature describing the association between eruptive cherry hemangiomatosis and MCD. The likely underlying mechanism is hypersecretion of vascular endothelial growth factor secondary to an elevated interleukin 6 level. Failure to recognize this association may have led to diagnostic delays. The authors suggest careful evaluation and follow-up of all patients presenting with the sudden onset of cherry hemangiomata, particularly with systemic symptoms, lymphadenopathy, or other benign vascular endothelial growths, for the potential development of MCD and other lymphoproliferative diseases.

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PHYSICIANS HAVE REPORTED cases of eruptive cutaneous lesions as manifestations of underlying hemato-oncologic diseases for more than a century.[1-6] Eruptions of cherry hemangiomata, glomeruloid hemangiomata, pyogenic granulomas, hypertrichosis lanuginosa, vellous hair cysts, steatocystomas, seborrheic keratoses, acquired ichthyosis, and keratoacanthoma have been associated with hematologic abnormalities and malignancies, including multiple myeloma, Hodgkin lymphoma, and POEMS (polyneuropathy, organomegaly, endocrinopathy, myeloma, and skin changes) syndrome.

We report a case of multicentric Castleman disease (MCD) presenting with multiple cherry hemangiomata and profound systemic symptoms during a 5-day period. This case represents an important association that has been infrequently reported in the literature. We propose a possible mechanism and suggest that patients presenting with eruptive cherry hemangiomatosis (ECH) in the setting of systemic symptoms should be fully evaluated for the potential development of MCD and other lymphoproliferative diseases.

REPORT OF A CASE

A 25-year-old man first presented in 2010 with a 2-month history of inguinal lymphadenopathy and 4.5-kg (10-lb) weight loss; a 5-day history of fatigue, right upper quadrant abdominal pain, "sudden appearance of blood moles," night sweats, and anorexia; and 2-day history of fevers and pleuritic chest pain. Physical examination disclosed 23 noncompressible, 0.1- to 0.5-cm, nontender, smooth, dome-shaped, bright-red vascular-appearing lesions over the trunk and upper limbs (**Figure 1**). Two of the lesions had an erythematous base. The clinical examination was compared with a patient-supplied photograph that confirmed patient and family member reports that the lesions were new and sudden in onset.

Corrected on February 27, 2014

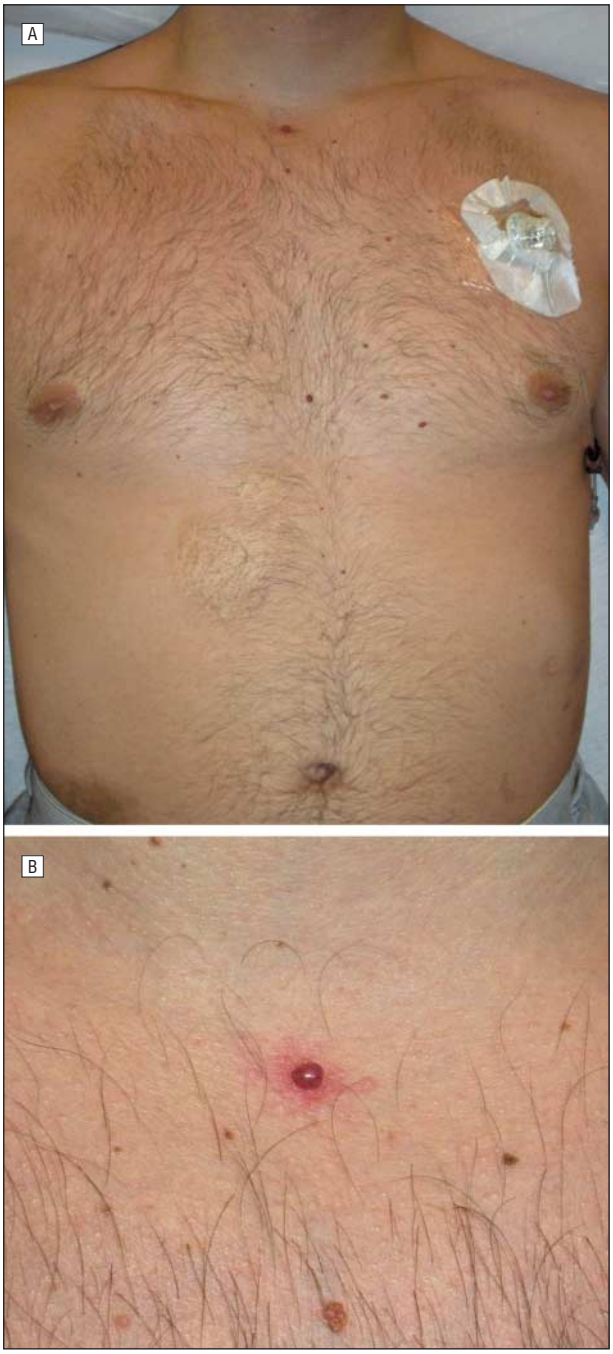

Figure 1. Eruptive vascuar proliferations noted on the patient's trunk and extremities. A, A 25-year-old man with cutaneous vascular eruptions on the trunk and upper extremities. B, A close-up view of a lesion at the suprasternal notch.

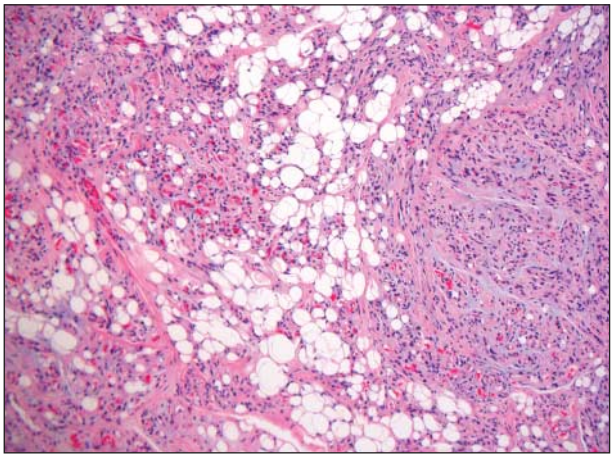

Figure 2. Angiolipoma biopsy specimen showing atypical vascular proliferations within lipomatous tissue (hematoxylin-eosin, original magnification ×40).

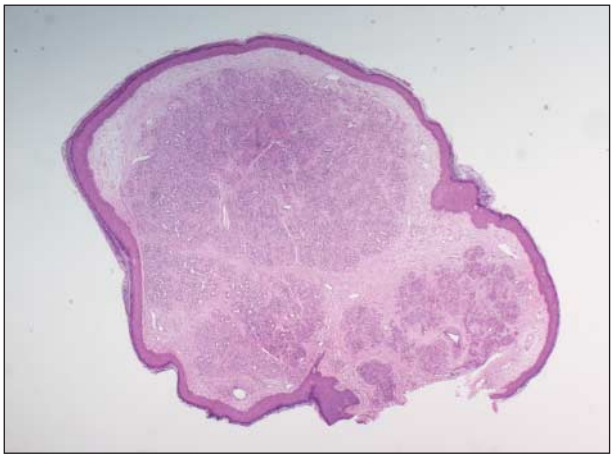

Figure 3. Skin biopsy specimen showing lobular proliferation of vessels with no atypia or abnormal infiltrates (hematoxylin-eosin, original magnification ×2).

Laboratory studies revealed a mildly elevated alkaline phosphatase level and mild thrombocytopenia. An abdominal ultrasonogram showed a hyperechogenic lesion in the liver interpreted as a benign hemangioma.

Medical history was pertinent for several benign vascular growths beginning up to 10 years before presentation. In 2000, a varicocele was discovered, repaired surgically, and then revised after a bypass vessel grew around the surgical occlusion. During a 2002 ophthalmic examination, an ophthalmologist noted highly vascularized retinas. Two separate dermatologists incidentally noted mild inguinal lymphadenopathy in 2005 and 2010. A 2.5-cm sigmoid tubular colonic adenoma, noted as "highly vascularized" by pathological report, caused significant lower gastrointestinal tract bleeding in 2009. One month prior to presentation, seven 1- to 2-cm subcutaneous masses, histopathologically consistent with angiolipomas, were noted on the patient's abdomen and flank (**Figure 2**).

Computed tomograms of the chest and abdomen showed ascites, pleural effusions, mediastinal and hilar lymphadenopathy, and splenomegaly. These findings were interpreted as a lymphoproliferative disorder or other hematologic malignancy. However, the fulminant clinical presentation was thought to be more consistent with a viral syndrome, and the radiologic abnormalities were considered reactive. The cutaneous eruptions were dismissed as being unassociated, and the patient was discharged with a presumed viral illness.

The patient returned the next day for a prolonged, 7-week hospitalization notable for multisystem organ failure, continued growth of his cutaneous vascular proliferations, left eye blindness caused by an acute retinal hemorrhage, hypoalbuminemia, anasarca, acute transaminitis,

Table. Multicentric Castleman Disease and Eruptive Cherry Hemangiomatosis Markers

Variable	Size of Eruptive Cherry Hemangiomata (Mean), cm	Total No. of New Eruptive Cherry Hemangiomata	Peak Levels		
			CRP, mg/L	IL-6, pg/mL	VEGF, pg/mL
Hospitalization for exacerbation 1	0.1-0.5 (0.3)	23	360	6	NM
Remission 1	0.1-0.2 (0.15)	5	NM	NM	NM
Hospitalization for exacerbation 2	0.2-0.7 (0.55)	3	NM	9	NM
Remission 2	0.1-0.5 (0.3)	0	10	6	348
Hospitalization for exacerbation 3	0.5-1.0 (0.75)	2	247	11.2	354
Remission 3	0.1-0.2 (0.15)	0	<0.5	7317[a]	48

Abbreviations: CRP, C-reactive protein; IL-6, interleukin 6; NM, not measured; VEGF, vascular endothelial growth factor.
SI conversion factor: To convert C-reactive protein from milligrams per liter to nanomoles per liter, multiply by 9.524.
[a] Following administration of siltuximab, interleukin 6 levels are no longer accurate or reliable, because the test measures levels of interleukin 6 complexed to the monoclonal antibody.

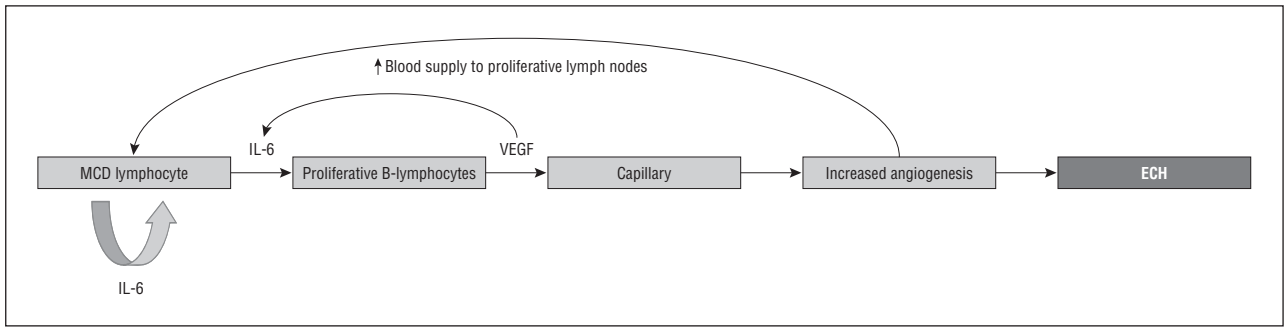

Figure 4. Mechanism of multicentric Castleman disease (MCD) to eruptive cherry hemangiomatosis (ECH). IL-6 indicates interleukin 6; VEGF, vascular endothelial growth factor.

anemia, and thrombocytopenia. Extensive infectious disease, rheumatologic, hematologic, and oncologic evaluations, excluding a lymph node biopsy, did not yield a diagnosis. High-dose methylprednisolone, administered empirically, brought about clinical improvement after 3 weeks. He was discharged without a diagnosis, and the vascular proliferations had decreased in size and faded in color.

Two weeks after discharge, the patient presented with 5 new vascular proliferations, growth of the previous lesions, and increasing inguinal lymphadenopathy. With hematoxylin-eosin staining, shave biopsy specimens revealed a polypoidal lobular proliferation of thin-walled vessels with no atypia, no abnormal infiltrates, and negative human herpesvirus 8 (HHV-8) staining, which were consistent with lobular capillary hemangiomata (**Figure 3**).

Biopsy specimens of enlarged inguinal and posterior cervical lymph nodes demonstrated human immunodeficiency virus–negative, HHV-8–negative mixed plasmacytic and hyaline vascular MCD.

The patient had a turbulent clinical course, including 2 prolonged hospitalizations in which clinical status, laboratory values, skin lesions, and lymphadenopathy waxed and waned in parallel (**Table**). The pertinent laboratory value peaks included a C-reactive protein level of 360 mg/L (reference range, 0-10 mg/L) (to convert to nanomoles per liter, multiply by 9.524), vascular endothelial growth factor (VEGF) level of 354 pg/mL (reference range, 9-86 pg/mL), interleukin 6 (IL-6) level of 12.3 pg/mL (reference range, 0-6 pg/mL), and interleukin 8 level of 241 pg/mL (reference range, 0-5). Additional pertinent laboratory studies included normal immunoglobulin levels, negative urine protein electrophoresis, negative serum protein electrophoresis, negative light chain restriction, negative fluorescent in situ hybridization/cytogenetics, negative cryoglobulins, and negative HHV-8 quantitative polymerase chain reaction. Hemangiomata diameter peaked at 0.5 to 1.0 cm. He was treated with a combination of rituximab, intravenous immunoglobulin, siltuximab (IL-6 monocolonal antibodies), bortezomib, methylprednisolone, thalidomide, doxorubicin hydrochloride, cyclophosphamide, and etoposide phosphate, yielding substantial improvement in clinical status, laboratory values, and cherry hemangioma involution. At 1 year after discharge, he has had no recurrence of either ECH or MCD.

COMMENT

Eruptive dermatologic lesions may be the first sign of an underlying hematologic disease. Specifically, erup-

tive cherry hemangiomata have been well documented to occur with various lymphoproliferative diseases.[7] To date, only 5 cases of eruptive capillary hemangiomata (including both cherry and glomeruloid types) have been reported with MCD, and they have all occurred in patients with MCD and POEMS syndrome.[8-11] Human herpesvirus 8 testing was performed in 2 of these cases; positive in one and negative in the other.

We present the first case (to our knowledge) of ECH as the presenting sign of MCD without associated POEMS syndrome. Furthermore, this is the first report that has documented other benign vascular growths occurring 10 years before overt presentation of MCD.

Multicentric Castleman disease is a lymphoproliferative disease involving multiorgan systems and aberrant levels of IL-6 production, which causes B-cell proliferation and secretion of VEGF.[12] An elevated VEGF level, in turn, stimulates further IL-6 secretion and angiogenesis within lymph nodes, systemically creating a microenvironment that promotes proliferation and disease progression.[13-15] Cherry hemangiomata and glomeruloid hemangiomata are benign cutaneous proliferations of capillaries that may erupt in MCD caused by the systemic hypersecretion of VEGF (**Figure 4**). In this and one other reported case, the hemangiomata regressed with treatment.[16] Eruptive cherry hemangiomatosis has also been described in patients with multiple myeloma, a lymphoproliferative malignancy in which IL-6 and VEGF levels are critical to pathogenesis.

The patient's clinical course and history suggest a relationship between MCD and ECH. Vascular endothelial growth factor, IL-6, and C-reactive protein levels were found to wax and wane in synchrony with the patient's clinical symptoms and vascular proliferations. The patient's medical history—a varicocele and subsequent bypass vessel growth after surgery, highly vascularized retinas, lower gastrointestinal tract bleeding secondary to a hypervascularized adenomatous polyp, angiolipomas (which resolved with MCD treatment), and a liver hemangioma (which resolved with MCD treatment)—is one of benign vascular proliferations potentially related to MCD. While several of these findings are common in the general population, their concomitance should raise concern of an underlying process. Furthermore, it is extremely uncommon for an adenomatous colonic polyp to have such extensive vascular proliferations and to cause overt gastrointestinal tract bleeding.[17-19] Thus, this patient's coexisting commonly observed growths as well as atypical benign vascular growths may have served as a clue for earlier diagnosis.

There are other possible causes for ECH in this patient, including previously described effects of atmospheric temperature, irritants, liver disease, graft-vs-host disease, and blockage of vessels by proteins or precipitates. However, the clinical course and corresponding cytokine profile in this patient would suggest that a disease-related factor, VEGF, is responsible for the dermatologic changes.

The pathogenesis of HIV-negative, HHV-8–negative MCD is unknown,[12] although a genetic mutation or immunomodulatory effects of an unidentified virus are the most likely mechanisms. The timescale of vascular anomalies in this patient with HIV-negative, HHV-8–negative MCD may lend insight into its pathogenesis. Systematic evaluation of other medical records of patients with MCD may provide important clues regarding pathogenesis.

In summary, we report an illustrative case involving 10 years of benign vascular growths and a 5-day history of ECH as the heralding signs of MCD. These findings have implications for the pathogenesis, diagnosis, surveillance, and evaluation of treatment response in MCD. Therefore, the dermatologic community should be aware of this important and rarely reported association. We suggest careful evaluation, including a lymph node biopsy, of all patients presenting with the sudden onset of cherry hemangiomata and systemic symptoms for the potential development of MCD and other lymphoproliferative diseases. Likewise, the involution or growth of cherry-red hemangiomata in a patient with MCD may serve as a surrogate marker of response to therapy or alternatively point to disease reactivation.

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Author Contributions: Mr Fajgenbaum had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Fajgenbaum and van Rhee. *Acquisition of data:* Fajgenbaum, Rosenbach, Nasir, and Reutter. *Analysis and interpretation of data:* Fajgenbaum, Rosenbach, and Nasir. *Drafting of the manuscript:* Fajgenbaum, van Rhee, and Nasir. *Critical revision of the manuscript for important intellectual content:* Fajgenbaum, Rosenbach, van Rhee, Nasir, and Reutter. *Administrative, technical, or material support:* Fajgenbaum and Rosenbach. *Study supervision:* Fajgenbaum, Rosenbach, van Rhee, and Nasir.
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Notable Notes

Hair Today, Gone Tomorrow: The Abandonment of Body Hair by American Women

Although the revival of the practice of body hair removal is a relatively recent trend in Western culture, this practice has deep roots in history. Rudimentary cave drawings depict beardless men hunting in the wild. Egyptian, Greek, and Roman men were known to shave their scalps and beard to avoid giving their enemy a handhold grip in battle. Alexander the Great ordered all of his men to shave their beards for this specific reason. Greek and Roman sculptures commonly depict hairless men and women, as this ideal was associated with class and civility.[1]

With the collapse of the Roman Empire, the practice of removing body hair did not become commonplace until the 1870s. In 1877, the American Dermatological Association was established. Afterward, this organization created the study of hypertrichosis, a problem seen to primarily affect young women. Men seldom were viewed as affected or required treatment.

This notion was further compounded by the July 1915 issue of *Harper's Bazaar*, which depicted a model without underarm hair. This publication incidentally coincided with Gillette's introduction of the first women's razor.[1] The trend of hair removal continued to gain popularity, and, by 1922, Sears catalogs regularly started printing underarm hair-removal advertisements. Sociologist Christine Hope[2] notes that concern for excessive hair increased tremendously between 1915 and 1945, as magazines became widely disseminated, and models portrayed an ideal of hairless feminine beauty. Changing fashion trends and the advent of the industrial revolution also popularized sleeveless and sheer evening gowns, as well as dresses with rising hemlines. Advertisements directly targeted this trend, with hair-removal advertisements stating, "Fashion Says—Evening gowns must be sleeveless or made with the merest suggestion of gauzy sleeves of tulle or lace. . . . The Woman of Fashion Says—The underarms must be as smooth as the face."[1] Hair-bearing areas, once confined to the intimacies of the bedroom, were now prominently displayed in the public's eye.

Since the 1980s, approximately 80% to 90% of women have been removing some type of hair from their bodies.[2] A century ago, hair removal was focused on the face and legs. Lately, men have also joined the trend and have begun shaving their armpits and other hair-bearing areas, colloquially known as "man-scaping." Still, some celebrities such as Mo'Nique, Julia Roberts, and Amanda Palmer proudly display their body hair, and a Lee Friedlander photographic print of an unshaven Madonna that appeared in *Playboy* in 1985 recently sold for $37 500.[3] Clearly, our body hair management practices have changed over short periods of time, and, perhaps, almost 100 years after the first advertisement appeared in *Harpers Bazaar*, a reversal of trends might be eminent.

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