Histopathology reveals a well-defined, nonencapsulated tumor affecting the dermis and, sometimes, the subcutaneous cellular tissue. In most lesions, a Grenz zone is visible with no involvement of the epidermis. The tumor is composed of spindle-shaped cell bundles with pale eosinophilic cytoplasm and basophilic nuclei. These cells are immersed in areas of dense hyaline collagen and other areas of myxoid stroma. In most cases, we can see mastocytes and small vessels. Cellular necrosis and lymphovascular invasion are not usually present.[1–8] Immunohistochemical staining is positive for CD34, CD99, and epithelial membrane antigen and negative for S-100, muscle-specific actin, and glial fibrillary acidic protein.[2–7]

Histologically, it is important to differentiate this tumor from cellular digital fibroma, a CD34-positive tumor composed of spindle-shaped cells with a less myxoid stroma than in acral fibromyxoma that does not show immunoreactivity for epithelial membrane antigen or CD99. The differential diagnosis also includes myxoid neurofibroma, superficial angiomyxoma, fibrous histiocytoma, dermatofibrosarcoma protuberans, and onychomatricoma, owing to the histological characteristics shared by these tumors (Table 1).

Treatment is based on surgical removal, although the tumor can recur in as many as 20% of cases if the excision is not complete.[2]

References

1. Fetsch J, Laskin W, Miettinen M. Superficial acral fibromyxoma: A clinicopathologic and immunohistochemical analysis of 37 cases of a distinctive soft tissue tumor with a predilection for the fingers and toes. Hum Pathol. 2001;32:704–14.
2. So-Min H, Ka-Hyung C, Kwang-Ryeol L, Yong-Hui J, Kim Song J. Superficial acral fibromyxoma on the second toe. Arch Plast Surg. 2013;40:477–9.
3. Messeguer F, Nagore E, Agusti-Mejias A, Traves V. Fibromixoma acral superficial, un tumor periungueal CD34 positivo. Actas Dermosifiliogr. 2012;103:67–81.
4. Martin B. Histopatología de la uña. Actas Dermosifiliogr. 2013;104:564–78.
5. Prescott RJ, Husain EA, Abdellaoui A, Al-Mahmoud RM, Khan M, Salman WD, et al. Superficial acral fibromyxoma: A clinicopathologic study of new 41 cases from the U.K: Should myxoma (NOS) and fibroma (NOS) continue as part of 21st-century reporting? Br J Dermatol. 2008;159:1315–21.
6. Hollmann TJ, Bovée JV, Fletcher CD. Digital fibromyxoma (superficial acral fibromyxoma): A detailed characterization of 124 cases. Am J Surg Pathol. 2012;36:789–98.
7. Al-Daraji WI, Miettinen M. Superficial acral fibromyxoma: A clinicopathological analysis of 32 tumors including 4 in the heel. J Cutan Pathol. 2008;35:1020–6.
8. Mahajan D, Billings SD, Goldblum JR. Acral soft tissue tumors: A review. Adv Anat Pathol. 2011;18:103–19.

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Mixed Connective Tissue Disease in a Patient With Castleman Disease and Hodgkin Lymphoma: Excellent Clinical Response to Rituximab[☆]

Enfermedad mixta del tejido conectivo en el contexto de enfermedad de Castleman y linfoma Hodgkin con excelente respuesta clínica a rituximab

To the Editor:

Castleman disease (CD), or angiofollicular lymphoid hyperplasia, is characterized by a process of reactive hyperplasia affecting the immune system. The condition can, therefore, give rise to a clinical picture similar to that of either a connective tissue disease or an autoimmune disease.[1] We report a case of Castleman disease and Hodgkin lymphoma in a patient who developed a mixed connective tissue disease (MCTD).

Case Description

The patient was a 49-year-old man, who had recently been diagnosed with Hodgkin lymphoma and multicentric Castleman disease and was being treated with adriamycin, bleomycin, vinblastine, and dacarbazine. He was referred to our department when he developed skin lesions and photosensitivity in association with Raynaud's phenomenon and muscle weakness a month after completing chemotherapy.

Physical examination revealed the following: erythematous-violaceous coloration on sun-exposed areas, elbows, and knees; edema of the palms and soles; and erythematous scaly papules on the dorsal surfaces of the interphalangeal and metacarpophalangeal joints of the hands consistent with Gottron papules (Fig. 1). Capillaroscopy demonstrated disorganization of the capillary bed, loss of normal capillary distribution, and a few thrombosed giant capillaries.

Two of the explorations performed yielded significant results: an electroneurogram evidenced sensory-motor polyneuropathy; and autoimmune tests revealed antinuclear antibodies (titers of 1:1280), anti-Smith antibodies, and

Figure 1   A, Erythematous-violaceous rash on the face and neck, which spares areas not exposed to sunlight, such as the lower eyelids and the submental area; alopecia due to chemotherapy also observed. B, Gottron papules on the metacarpophalangeal and interphalangeal joints. C, Edema in the soles of both feet. D, Swollen palms and sausage fingers.

anti-U1 ribonucleoprotein (U1-RNP) (titers > 1:1.600). The results of other autoantibody tests were negative. Histological study of biopsied samples of skin and muscle tissue from the arm revealed vacuolization of the basal layer and thickening of the basement membrane as well as a positive periodic acid-Schiff stain (Fig. 2) and signs of inflammatory myositis. These findings led to a diagnosis of MCTD associated with Castleman disease and Hodgkin lymphoma. In view of the reported association between Castleman disease and the human immunodeficiency virus and the human herpesvirus 8, serology was performed to screen for these viruses, with negative results in both cases. The negative result for the human herpesvirus 8 was confirmed by a polymerase chain reaction assay in peripheral blood, in which no viral load was detected.

Initial treatment with corticosteroids and antimalarials had little effect on the symptoms of MCTD, but subsequent treatment with rituximab achieved remission of both MCTD and Castleman disease. The regimen used was 375 mg/m^2 administered intravenously once a week for 4 weeks, with a repeat cycle after 6 months, in combination with methylprednisolone 7.5 mg/d (Fig. 3).

Discussion

MCTD was first described in 1972 as a disorder characterized by a combination of the clinical features of systemic lupus erythematosus, systemic scleroderma, polymyositis/dermatomyositis, and rheumatoid arthritis in the presence of high titers of anti-U1-RNP.[2] The most common clinical manifestations include Raynaud's phenomenon, swollen hands, fingers with a sausage appearance, joint pain, and muscle weakness. The cutaneous manifestations include features consistent with a dermatomyositis-like or
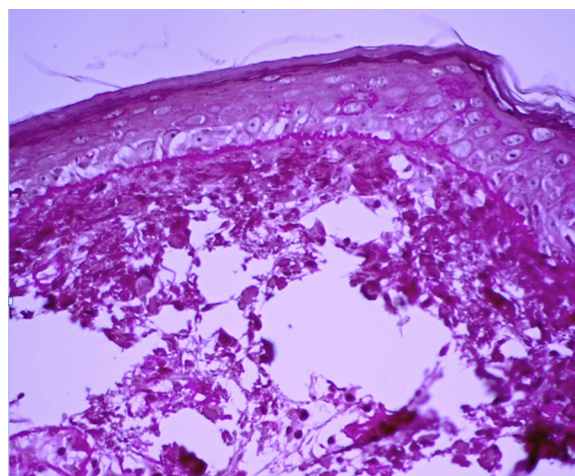

Figure 2   Basal layer vacuolization and thickening of the basement membrane (periodic acid-Schiff ×20).
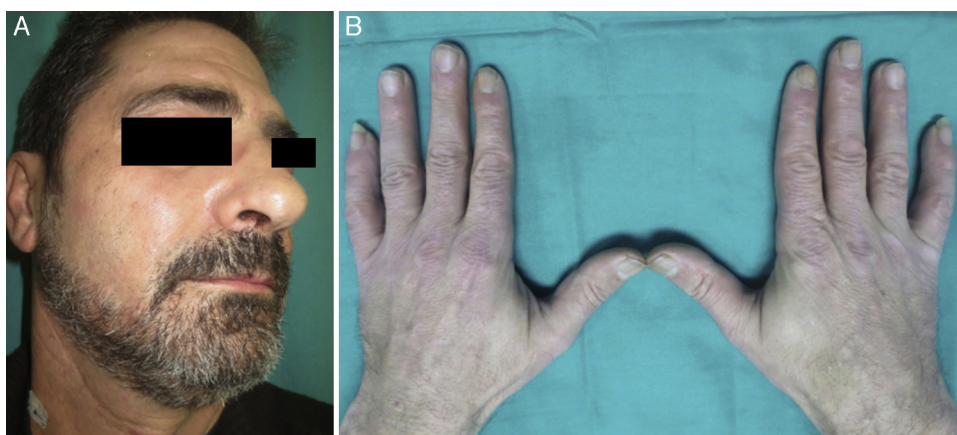
Figure 3 A, Resolution of the facial rash following treatment with rituximab. B, Appearance of hands after treatment.

systemic lupus erythematosus-like photosensitivity, ulcers, Sjogren syndrome, and urticarial vasculitis, although no specific or pathognomonic clinical finding has been identified.[3]

The diagnostic criteria proposed by Alarcón-Segovia et al.[4] have a sensitivity of 100%. For a confirmed diagnosis, the patient must fulfill the serologic criteria (anti-U1-RNP autoantibodies with a titer in hemagglutination of > 1:1600) and at least 3 of the clinical criteria, which are swollen hands, synovitis, myositis, Raynaud's phenomenon, and acrosclerosis.

There have been several reports of patients with Castleman disease presenting autoimmune manifestations, with more cases of hemolytic anemia and fewer of connective tissue disease. The onset of autoimmune manifestations has been reported as occurring both before and after the onset of Castleman disease. To date, only 3 cases of MCTD associated with Castleman disease have been reported in the literature. Nanki et al.[5] reported the case of a 60-year woman with multicentric Castleman disease and EMTC in which pharmacological remission was achieved following treatment with melphalan; Chrispal et al.[6] reported associated EMTC and Castleman disease in a 16-year-old girl; and Hosaka et al.[7] reported 3 cases of Castleman disease mimicking the features of collagen disease, one of them with symptoms typical of MCTD. No association with Hodgkin lymphoma was reported in any of these cases.

In the case of our patient, the treatment chosen was the anti-CD20 agent rituximab because an increased mean survival has been reported in patients with Castleman disease on rituximab-based therapies, although there is less experience on the use of this therapy in EMTC.[8] Remission of the clinical manifestations of subacute lupus has been reported in patients with MCTD as well as improvement in refractory thrombocytopenia and Raynaud's phenomenon; the only adverse effect reported in these patients treated with rituximab was 1 case of severe ischemia.[9–11] The therapeutic mechanism of rituximab involves depletion of CD20 positive cells, which are its therapeutic target. CD20 positive cells are directly or indirectly responsible for the dysregulated production of interleukin-6 and other cytokines.

In this case it appears that 3 diseases may be related. Overproduction of interleukin 6 by Reed-Sternberg cells and histiocytes in Hodgkin lymphoma has been demonstrated, and this abnormal immune state is responsible for the association between Hodgkin lymphoma and Castleman disease.[12] The resulting proinflammatory cytokine microenvironment may trigger an exaggerated immune response, leading to a loss of tolerance and the development of an autoimmune disease.[13]

Bibliografía

1. De Marchi G, de Vita S, Fabris M, Scott CA, Ferraccioli G. Systemic connective tissue disease complicated by Castleman's disease: Report of a case and review of the literature. Haematologica. 2004;89:ECR03.
2. Ortega-Hernandez OD, Shoenfeld Y. Mixed connective tissue disease: An overview of clinical manifestations, diagnosis and treatment. Best Pract Res Clin Rheumatol. 2012;26:61–72.
3. Burdt MA, Hoffman RW, Deutscher SL, Wang GS, Johnson JC, Sharp GC. Long-term outcome in mixed connective tissue disease: Longitudinal clinical and serologic findings. Arthritis and Rheumatism. 1999;42:899–909.
4. Alarcón-Segovia D, Villareal M. Classification and diagnostic criteria for mixed connective tissue disease. In: Kasukawa R, Sharp GC, editors. Mixed connective tissue disease and antinuclear antibodies. Amsterdam: Elsevier; 1987. p. 33–40.
5. Nanki T, Tomiyama J, Arai S. Mixed connective tissue disease associated with multicentric Castleman's disease. Scand J Rheumatol. 1994;23:215–7.
6. Chrispal A, Vasuki Z, Thomas EM, Boorugu HK. Mixed connective tissue disorder and Castleman's disease. J Assoc Physicians India. 2010;58:515–7.
7. Hosaka S, Kondo H. Three cases of Castleman's disease mimicking the features of collagen disease. Ryumachi. 1994;34:42–7.
8. Hoffmann C, Schmid H, Müller M, Teutsch C, van Lunzen J, Esser S, et al. Improved outcome with rituximab in patients with HIV-associated multicentric Castleman disease. Blood. 2011;118:3499–503.
9. Fantó M, Salemi S, Socciarelli F, Bartolazzi A, Natale GA, Casorelli I, et al. A case of subacute cutaneous lupus erythematosus in a patient with mixed connective tissue disease: Successful treatment with plasmapheresis and rituximab. Case Rep Rheumatol. 2013;2013:857694.
10. Jovancevic B, Lindholm C, Pullerits R. Anti B-cell therapy against refractory thrombocytopenia in SLE and MCTD patients: Long-term follow-up and review of the literature. Lupus. 2013;22:664–74.
11. Vela P, Sivera F, Battle-Gualda E, Mayor M, García Manzanares A, Pascual E. Severe ischemia following treatment with rituximab

in a patient with mixed connective tissue disease: An unusual complication. Lupus. 2010;19:1005–6.

12. Falchi L, Capello D, Palumbo B, Rauco A, Emili R, Cianciulli M, et al. A case of nodular sclerosis Hodgkin's lymphoma repeatedly relapsing in the context of composite plasma cell-hyaline vascular Castleman's disease: Successful response to rituximab and radiotherapy. Eur J Haematol. 2007;79:455–61.

13. Straub RH, Besedovsky HO. Integrated evolutionary immunological neuroendocrine framework for the pathogenesis of chronic disabling inflammatory F diseases. FASEB J. 2003;17:2176–83.

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Are We Examining Our Patients Properly and Can We Do a Better Job?[☆]

CrossMark

¿Exploramos correctamente a los pacientes? ¿Qué nos está pasando?

To the editor:

Melanoma remains a prominent health concern. It is one of the most frequent tumors in young adults.[1] The incidence and associated mortality has increased in recent decades.[2–4]

Although metastatic melanoma can only be cured on limited occasions, new immunotherapy treatments[5–7] (for example, high-dose IL-2, ipilimumab [anti-cytotoxic T-lymphocyte antigen 4], pembrolizumab, and nivolumab [anti-programmed cell death 1], etc.) and combination treatments for specific mutations[8,9] (BRAF, mitogen-activated protein kinase [MEK], and c-KIT inhibitors) have increased survival for patients with stage III and IV disease. At times, melanoma is diagnosed in an advanced phase and a primary tumor is not detected despite exhaustive study. Metastatic melanoma from an unknown primary tumor is defined as the histologically confirmed presence of melanoma in a lymph node, organ, or other tissue without history or evidence of a primary skin, mucosal, or ocular lesion. These metastatic lesions are estimated to comprise 3.2% of all melanomas and they seem to have a better prognosis than those metastatic lesions of known origin.[10]

We present the cases of 2 patients seen initially in tertiary hospitals with metastatic melanoma of unknown origin who sought a second opinion in our hospital.

Case Histories

A 67-year-old man was seen in his local hospital with swollen lymph nodes in his left groin. After histologic and immunohistochemical study of one of the swollen lymph nodes, metastatic melanoma of unknown origin was diagnosed. The patient was assessed by an oncologist and a dermatologist, who were unable to locate the primary melanoma. Given that immunotherapy treatment was contraindicated and the BRAF mutation was absent, he received 3 chemotherapy sessions for several months. We are awaiting a reduction in the inguinal mass before palliative lymphadenectomy.

By coincidence, in the same week, we assessed the second patient. He was 45 years old, and had a large and rapidly growing tumor in the left laterocervical region that prompted him to attend his reference hospital. Histologic and immunohistochemical study of the mass pointed to diagnosis of metastatic melanoma. The lesion was positive for the BRAF mutation. In the study of extension by computed tomography-positron emission tomography, lymph node metastases were also found at other sites. After multidisciplinary assessment by an oncologist, a dermatologist, an ear-nose-throat specialist, and a ophthalmologist, he was diagnosed with metastatic melanoma of unknown origin and prescribed treatment with a BRAF inhibitor (vemurafenib) and a MEK inhibitor (trametinib).

After taking the medical history and the physical examination of the patients, the primary tumor was located in both patients: the first patient had a dark, keratotic pigmented lesion measuring 1.5×1 cm, with the Hutchinson sign, on the ball of the left big toe (Fig. 1). The second patient had a hyperpigmented lesion measuring 2×1.5 cm in diameter in the left parietal region, with a characteristic atypical dermoscopic pattern (Fig. 2). In both cases, the lesion was evident and was located on a region of the skin that should be examined given the site of the lymph node metastasis. Certain care in the examination was, however, required because the lesion was located on an area of the scalp covered by hair in one case and in the acral most part of the body in the other.

We present 2 cases that may well reflect other avoidable situations in dermatology departments in our hospitals. Although this may appear a diagnostic omission and would have no bearing on the follow-up and therapeutic approach, prognosis does vary according to whether the primary tumor is known or unknown.[10]

A detailed medical history and careful physical examination are the basis for diagnosis. A study in the United States concluded that the percentage of dermatologists who perform a complete examination of patients with risk factors for melanoma does not exceed 50%.[11] Other studies