that interferon beta-1a could stimulate CD8+ lymphocytes to recognize melanocyte-derived proteins; these cells are known to play a key role in vitiligo. Several cases of vitiligo with the use of interferon alpha-2a have also been described.[8]

Although the exact pathophysiology of halo nevi and vitiligo is unknown, the 2 manifestations appear to have a common pathophysiology and often present together. Several theories suggest that these manifestations are the result of an immune response against melanocytes, probably mediated by CD8+ cell activation, as might occur with the use of interferon.

A literature review found 2 reports of drug-induced multiple halo nevi of sudden onset with the use of infliximab and imatinib.[9,10] In the first case, the condition was associated with worsening of previous alopecia areata, and the authors proposed that anti-TNF drugs induce autoimmune phenomena that include alopecia areata and halo nevi. In the second case, there was a relationship with c-Kit tyrosine kinase inhibition.

In conclusion, our patient developed multiple halo nevi a few weeks after the start of interferon therapy. We believe that in our patient there was a relationship between the use of interferon and the development of multiple halo nevi, due to the temporal association and the immune system modifications that this therapy induces through CD8+ cell activation, favoring autoimmune phenomena; this is an important event in the pathophysiology of the development of halo nevi. The use of systemic or intralesional interferon has been shown to shrink or eliminate some melanoma metastases, probably by the same mechanism that induces the formation of halo nevi and vitiligo. This highlights the importance of immunity in the biology of melanocytic lesions and opens the door to possible therapeutic approaches to melanoma treatment.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Jonasch E, Haluska FG. Interferon in oncological practice: review of interferon biology, clinical applications and toxicities. Oncologist. 2001;6:34–55.
2. Zeff RA, Freitag A, Grin CM, Grant-Kels JM. The immune response in halo nevi. J Am Acad Dermatol. 1997;37:620–4.
3. Wenzel J, Bekisch B, Uerlich M, Haller O. Type I interferon-associated recruitment of cytotoxic lymphocytes. A common mechanism in regressive melanocytic lesions. Am J Clin Pathol. 2005;124:37–48.
4. Gold R, Rieckmann P, Chang P, Abdalla J. The long-term safety and tolerability of high-dose interferon beta-1a in a relapsing-remitting multiple sclerosis: 4-year data from the PRISMS study. Eur J Neurol. 2005;12:649–56.
5. Duchini A. Autoimmune hepatitis and interferon beta-1a for multiple sclerosis. Am J Gastroenterol. 2002;97:767–8.
6. Speciale L, Saresella M, Caputo D, Ruzzante S, Mancuso R, Calvo MG, et al. Serum autoantibodies presence in multiple sclerosis patients treated with beta-interferon 1a and 1b. J Neurovirol. 2000;6:S57–61.
7. Kocer B, Nazliel B, Oztas M, Batur HZ. Vitiligo and multiple sclerosis in a patient treated with interferon beta-1a: a case report. Eur J Neurol. 2009;19:78–9.
8. Seckin D, Durusoy C, Sahin S. Concomitant vitiligo and psoriasis in a patient treated with interferon alfa-2a for chronic hepatitis B infection. Pediatr Dermatol. 2004;21:577–9.
9. Fabre C, Dereure O. Worsening alopecia areata and the novo occurrence of multiple halo nevi in a patient receiving infliximab. Dermatology. 2008;216:185–6.
10. Fava P, Stroppiana E, Savoia P, Bernengo MG. Halo nevi related to treatment with imatinib in a dermatofibrosarcoma protuberans patient. JEADV. 2010;24:244–5.

E. Vera-Iglesias,* M. García-Arpa, P. Sánchez-Caminero

F.E.A. Servicio de Dermatología, Hospital General de Ciudad Real, Ciudad Real, Spain

* Corresponding author.
E-mail address: everaigl@hotmail.com (E. Vera-Iglesias).

doi:10.1016/j.adengl.2011.02.005

Anogenital Granulomatosis☆

Granulomatosis anogenitales

To the Editor:

Chronic recurrent granulomatous processes in the anogenital area present with ulcers, fissures, and lymphedema; histopathology reveals nonnecrotizing granulomatous inflammation. Crohn disease is the most common etiologic factor, but cases in which no underlying cause is evident have been grouped under the term anogenital granulomatosis.[1]

☆ Please cite this article as: Villar M, Petiti G, Guerra A, Vanaclocha F. Granulomatosis anogenitales. Actas Dermosifiliogr. 2012;103:76–79.

The first case we report is that of a 52-year-old woman with excrescent lesions that had a pseudocondylomatous appearance and fissures in the gluteal cleft that had started 6 months earlier. The lesions were excised but she did not return until 5 years later, when she sought care for chronic recurrent vulvar and perineal lesions. She had ulcers, marked edema of the vulva, longitudinal fissures in the folds, and indurated plaques that were excrescent in the gluteal cleft (Fig. 1). Histopathology of both the vulvar and the perianal areas revealed a lymphocytic infiltrate in the reticular dermis with nonnecrotizing granulomas consisting of multinucleated giant cells (Fig. 2A and B). Additional tests, including complete blood count, biochemistry, chest radiograph, and cultures yielded no findings, except for an elevated erythrocyte sedimentation rate (ESR) of 52 mm/h. A colonoscopy with colorectal biopsies ruled out inflammatory bowel disease. The patient was treated with topical corticosteroids, salicylates, and oral corticos-

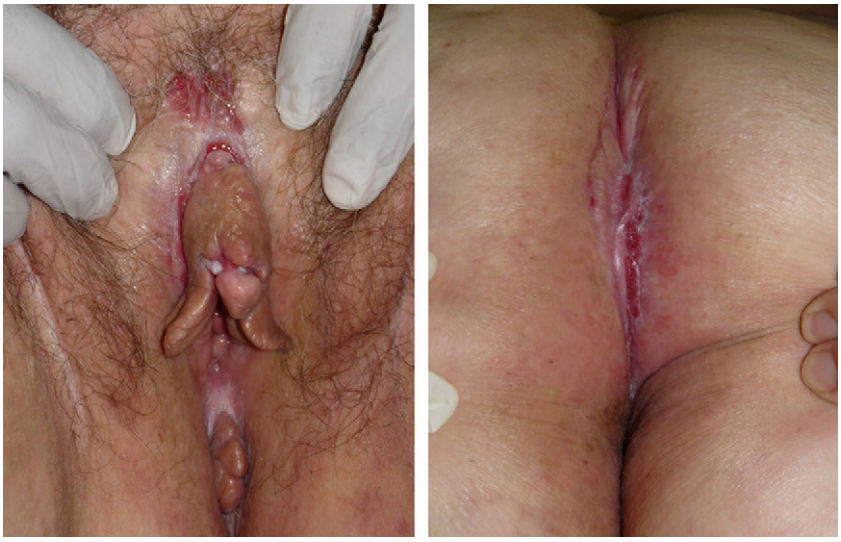

Figure 1 Vulva, showing numerous ulcers, fissures arranged longitudinally in the folds, and edema of the labia majora, labia minora, and clitoral hood. In the gluteal cleft, excrescent plaques with a pseudocondylomatous appearance and longitudinal cracks.

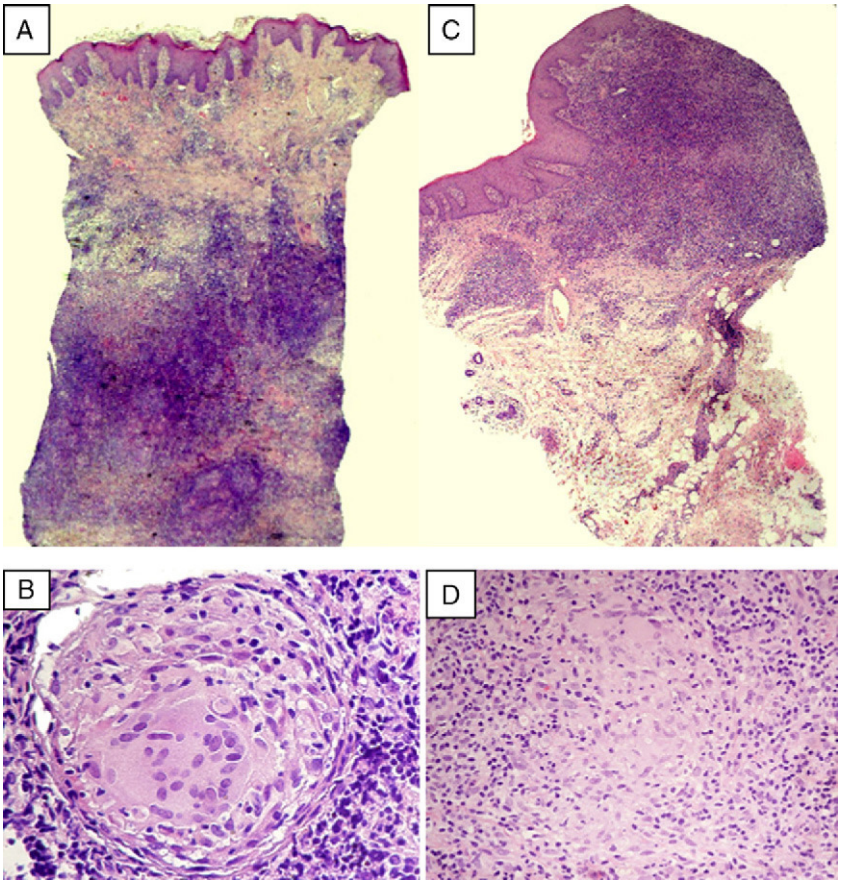

Figure 2 (A) Lymphocytic infiltrate occupying the reticular dermis, showing granulomatous structures without central necrosis (hematoxylin–eosin, original magnification ×12.5). (B) Detail of a granuloma composed of multinucleated giant cells and epithelioid cells and surrounded by lymphocytes (hematoxylin–eosin, original magnification ×400). (C) Dense lymphocytic infiltrate occupying a mucous membrane (hematoxylin–eosin, original magnification ×40). (D) At higher magnification, epithelioid cells are seen forming nonnecrotizing granulomas (hematoxylin–eosin, original magnification ×400).

teroids; the lesions responded fully to the last treatment but recurred when they were suspended. She was subsequently treated with adalimumab (40 mg/15 d) but showed no response after 4 months. Fifteen years after the initial episode the patient had not developed systemic symptoms.

The second case is that of a 51-year-old woman who presented with painful erosions and vulvar edema dating from 5 months earlier. For 6 years she had also had recurrent perianal suppurative plaques and fissures that had been diagnosed as hidradenitis suppurativa. Physical examination revealed the granulomatous appearance of the vulvar mucosa, erosions on the inside of the labia minora (Fig. 3), and longitudinal fissures in the gluteal cleft. Two vulvar biopsies revealed a dense lymphocytic infiltrate of epithelioid cells and multinucleated giant cells forming granulomas without central necrosis (Fig. 2C and D). Additional tests (complete blood count, biochemistry, cultures, and chest radiograph) were normal or negative, except for a slightly elevated ESR of 25 mm/h. Crohn disease was ruled out after colonoscopy with biopsies. The patient had no systemic symptoms during the 18 months of follow-up and responded partially to treatment with oral corticosteroids but showed no response to salicylates or to adalimumab (40 mg/15 d), which was therefore suspended after 3 months.

The differential diagnosis of chronic granulomatous diseases in the perineum includes extraintestinal Crohn disease, although this condition is unlikely in the absence of intestinal symptoms or perianal fistulas and with normal colonoscopy.[2] Other possible differential diagnoses are shown in Table 1. In view of the clinical presentation, the first diagnostic steps should be biopsy to obtain a specimen for histology (on the basis of special stains and cultures for fungi, bacteria, and mycobacteria). Additional tests useful to rule out underlying causes include complete blood count, biochemistry, iron profile, ESR, angiotensin-converting enzyme levels, serology for syphilis, and chest radiograph. Colonoscopy is recommended, even in the absence of digestive symptoms.

Chronic genital granulomatosis without direct communication with the gastrointestinal tract can be observed in metastatic Crohn disease. This condition is the least common cutaneous manifestation of Crohn disease and consists of skin lesions separated from the digestive tract by healthy skin. It usually affects women between the second and fourth decades of life and can appear anywhere, including on the genitals, although the lower limbs are the most frequent location.[3] Clinical manifestations in the genital region are similar to those observed in our patients.[4] Lesions are associated with involvement of the colon or rectum[5] but usually do not follow a course that runs parallel to the intestinal disease. Chronic genital granulomatosis is associated with long-standing intestinal Crohn disease in 80% of cases.[3,6] When the granulomatous process presents first, intestinal involvement usually develops within 4 months to 2 years. The literature offers at least 5 cases[3] of cutaneous Crohn disease in the absence of previously recognized intestinal disease, which did not appear during follow-up either. Some authors nonetheless recommend reserving this diagnosis for cases in which intestinal involvement has been demonstrated.[7]

Orofacial granulomatosis or cheilitis granulomatosa, considered a monosymptomatic form of Melkersson–Rosenthal syndrome, shares some of the clinical and histological features of the anogenital granulomatosis in our 2 cases. Cheilitis granulomatosa presents as persistent and recurrent labial swelling; nonnecrotizing granulomas are sometimes associated with ulceration and gingival hyperplasia or cob-

Table 1 Differential Diagnosis of Anogenital Granulomatosis.

Noninfectious Causes	Infectious Causes
Crohn disease	Tuberculosis
Sarcoidosis	Lymphogranuloma venereum
Foreign body granuloma	Granuloma inguinale
Hidradenitis suppurativa	Syphilis
Behçet disease	Leprosy
Pyoderma gangrenosum	Deep mycoses
Lymphoproliferative diseases	
Melkersson–Rosenthal syndrome	

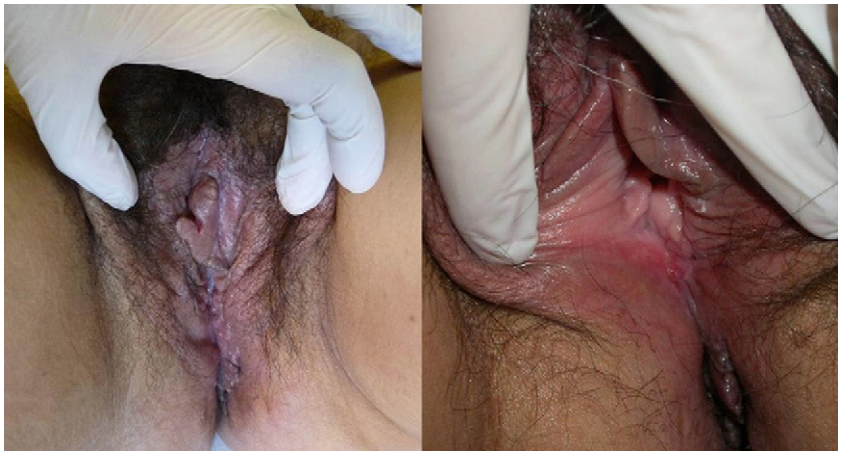

Figure 3 Edematous vulvar mucosa, with a granulomatous appearance. Erosions on the inner surface of the labia minora.

blestoning. Anogenital granulomatosis has been suggested to be the genital equivalent of cheilitis granulomatosa[2] and although the co-occurrence of these 2 conditions in the same patient is rare, it has been reported.[7] In 10%–48% of cases cheilitis granulomatosa and intestinal Crohn disease are associated.[8]

The term anogenital granulomatosis[1] was introduced in 2003 to identify these chronic recurrent conditions with characteristic clinical and histopathologic features that may have different causes. This clinical entity is a unifying concept for others used in the literature (chronic hypertrophic vulvitis, vulvitis granulomatosa, chronic edema of the vulva, Melkersson–Rosenthal vulvitis and anoperineitis granulomatosa) and is especially useful for cases of unknown etiology and those highly suggestive of metastatic Crohn disease in the absence of established intestinal disease.

Therapeutic management of this condition is difficult and there is no set protocol to follow because of the lack of case series and randomized trials. Suggested treatments have obtained mixed and sometimes unsatisfactory results marked by frequent relapse after treatment is discontinued. The reported options include topical, intralesional, and oral corticosteroids,[7] salicylates, antibiotics[9] such as metronidazole[5,10] and ciprofloxacin,[4] and immunosuppressants such as azathioprine and ciclosporin.[1,3] More recently, anti-tumor necrosis factor monoclonal antibodies such as infliximab and adalimumab have given good results.[1]

We have reported 2 cases of idiopathic anogenital granulomatosis in which possible underlying causes were ruled out and no associated systemic symptoms developed even after years of follow-up.

References

1. van der Scheur MR, van der Waal RI, van der Waal I, Stoof TJ, van Deventer SJ. Ano-genital granulomatosis: the counterpart of oro-facial granulomatosis. J Eur Acad Dermatol Venereol. 2003;17:184–9.
2. Hackel H, Hartmann AA, Burg G. Vulvitis granulomatosa and anoperineitis granulomatosa. Dermatologica. 1991;182:128–31.
3. Palamaras I, El-Jabbour J, Pietropaolo N, Thomson P, Mann S, Robles W, et al. Metastatic Crohn's disease: a review. J Eur Acad Dermatol Venereol. 2008;22:1033–43.
4. Gómez-Centeno P, Casas L, Valdés-Tascón F, Peteiro C, Toribio J. Enfermedad de Crohn metastásica: a propósito de un caso con afectación vulvar. Actas Dermosifiliogr. 1999;90:100–3.
5. Bel Pla S, García-Patos Briones V, García Fernández D, Aparicio Español G, Castells Rodellas A. Linfedema vulvar: una manifestación infrecuente de la enfermedad de Crohn metastásica. Gastroenterol Hepatol. 2001;24:297–9.
6. Shannon L, Corbett SL, Walsh CM, Spitzer RF, Ngan BY, Kives S, et al. Vulvar inflammation as the only clinical manifestation of Crohn disease in an 8-year-old girl. Pediatrics. 2010;125:e1518–22.
7. Thiriar S, Deroux E, Dourov N, Evrard L, Peny MO, Simon P, et al. Granulomatous vulvitis, granulomatous cheilitis: a single diagnosis? Dermatology. 1998;196:455–8.
8. Bogenrieder T, Rogler G, Vogt T, Landthaler M, Stolz W. Orofacial granulomatosis as the initial presentation of Crohn's disease in an adolescent. Dermatology. 2003;206:273–8.
9. Fenniche S, Mokni M, Haouet S, Ben Osman A. Maladie de Crohn vulvaire: 3 observations. Ann Dermatol Venereol. 1997;124:629–32.
10. Roé E, Barnadas MA, Bergua P, Sancho F, Matas L, Paredes R, et al. Anogenital granulomatosis treated with ciprofloxacin. J Eur Acad Dermatol Venereol. 2009;23:89–90.

M. Villar,* G. Petiti, A. Guerra, F. Vanaclocha

Servicio de Dermatología, Hospital Universitario 12 de octubre, Madrid, Spain

*Corresponding author.
E-mail address: mariavb20@hotmail.com (M. Villar).

doi:10.1016/j.adengl.2011.05.007

Atypical Calciphylaxis Secondary to Treatment With Acenocoumarol☆

Calcifilaxia atípica secundaria al tratamiento con acenocumarol

To the Editor:

Calciphylaxis is a rare disease characterized by cutaneous ischemia and necrosis caused by mural calcification of small and medium-sized blood vessels.[1] This condition leads to cutaneous ulceration and eschar formation. It generally affects patients with end-stage renal failure and secondary hyperparathyroidism,[1–3] and is associated with a poor prognosis, high morbidity, and high mortality rates.[1–4] In recent years, cases have been reported of calciphylaxis in patients with normal kidney function and calcium–phosphate metabolism.[4–7] When seen in patients without abnormalities of this sort—a rather rare occurrence—the condition is called atypical calciphylaxis.[6] It has occasionally been reported in patients receiving oral anticoagulant therapy with coumarin derivatives, such as warfarin and phenprocoumon.[3,4,6,7]

We present the case of an 80-year-old woman who came to our hospital with purpuric skin lesions in a livedoid pattern that had appeared 2 months earlier on the back of the right leg. The lesions were associated with induration and intense local pain. Several weeks after the onset of the first symptoms, the patient noticed the appearance of an ulcer, which was quickly covered by necrotic eschar. Similar intensely painful skin lesions began to appear on the left leg at the same time.

☆ Please cite this article as: Álvarez-Pérez A, Gutiérrez-González E, Sánchez-Aguilar D, Toribio J. Calcifilaxia atípica secundaria al tratamiento con acenocumarol. Actas Dermosifiliogr. 2012;103:79–81.