To the Editor:

Bowen disease is described as an in situ squamous cell carcinoma that, like other skin tumors, can present as a pigmented tumor, thereby necessitating differential diagnosis with other pigmented tumors.1-6

We present the case of a 48-year-old woman with no relevant personal or family history who was referred to the melanoma unit of our department with suspected diagnosis of “perianal melanoma.” She reported that the lesion had appeared approximately 3 years earlier and that it had been growing slowly ever since. Physical examination of the perianal region revealed an asymmetric poorly demarcated multicolor pigmented tumor that measured 3.5 × 2 cm and that was covered with whitish scales (Figure 1). In the dermoscopic examination (FotoFinder system), the only feature characteristic of melanoma was an aggregate of globules of irregular shapes and sizes in one part of the tumor; reticular pigmentation pattern, starburst pattern, and other features indicative of melanoma were not found. In the rest of the tumor, an atypical vascular pattern was observed comprising large, tortuous, irregular structures, some of which were rounded. In the lower part of the lesion, a verrucous whitish surface could be discerned. Biopsy showed a tumor confined to the epidermis with acanthosis, a certain degree of papillomatosis, markedly atypical cells, and mitotic figures, with a completely intact basement membrane. Immunohistochemical studies using markers such as Melan-A and pancytokeratin cocktail confirmed the nature of the tumor, which was diagnosed as a case of pigmented Bowen disease. We excised the lesion and, 18 months after the procedure, the patient remains asymptomatic.

Bowen disease is a relatively common tumor that is considered to be an intraepidermal squamous cell carcinoma.1-3,6 The pigmented forms of this tumor—although uncommon (less than 2% of cases1,5)—require differential diagnosis with other pigmented tumors and with melanoma in particular. Although pigmented Bowen disease can appear at any site, it is rarely found in the genital region, and only 3 cases have been described in the literature to date.1,4,7 Various etiologic factors have been implicated in the development of the disease, including chronic exposure to UV radiation and arsenic,1,2 trauma, ionizing radiation, and human papillomavirus (HPV) infection. Indeed, HPV infection is particularly important in the development of tumors at sites not exposed to sunlight or in areas often infected by the virus, such as the perigenital region.

Dermoscopy is a noninvasive technique that improves diagnostic accuracy in the case of pigmented lesions. Several dermoscopic features of Bowen disease have been described.2,3,8-10 The most characteristic and common findings for this tumor are shown in the Table. The most frequently observed such feature in Bowen disease is the multicomponent pattern.8 Of the criteria presented in the Table, the most specific to Bowen disease are presence of atypical vascular...
Eosinophilic Fasciitis After Taking Simvastatin

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To the Editor:

Eosinophilic fasciitis is a rare fibrosing disease characterized by painful, symmetric inflammation of the limbs, and progressive induration of the skin. In some cases, it can also lead to debilitating joint contractures, arthritis, neuropathy, and myositis. The hallmark histologic finding is fascial fibrosis. While eosinophilic fascitis is considered by some to be a variant of morphea or scleroderma, others believe it to be a separate entity. The condition is of unknown etiology but it has been associated with a variety of disease processes as well as with exposure to environmental factors, toxins, and certain drugs.

We present the case of a 71-year-old woman with a history of osteoporosis under treatment with bisphosphonates and primary hypercholesterolemia under treatment with simvastatin.

The patient presented with progressive induration of the skin on her arms and legs that had appeared 9 months earlier. She also had asthenia and dyspnea on moderate exertion. The symptoms had appeared 3 weeks after initiation of simvastatin and worsened progressively until the drug was withdrawn 1 month later. The symptoms then stabilized but did not improve.

References

Physical examination revealed erythema, induration, and dimpling of the skin on the arms and, particularly, on the legs (Figure 1). There was no evidence of acrosclerosis or of any other skin lesions.

The only other remarkable findings in the laboratory workup were slight eosinophilia (0.65 × 10^9/L) and an elevated erythrocyte sedimentation rate (27 mm/h). All other blood count and biochemistry test results were normal, and the results of serology tests and analysis of rheumatoid factor were negative.

A biopsy of the deep skin layers revealed fibrosis involving the reticular dermis, the septa of the superficial fascia, and reaching the striated muscle; there was also a perivascular and interstitial lymphocytic infiltrate (Figure 2).

Because the clinical and histology findings were suggestive of eosinophilic fasciitis, the patient was administered prednisone (60 mg/d) and methotrexate (5 mg/wk), leading to a gradual improvement of symptoms.

Although the cause of eosinophilic fasciitis is unknown, there are several reports of patients developing it after intense physical exercise. It has also been associated with various hematologic diseases, kidney diseases, infections by *Borrelia burgdorferi*, and the administration of certain drugs.

In our case, the fact that the onset of symptoms was temporally associated with the use of simvastatin and that there were no other potential causative factors suggests that this drug might have triggered the condition.

Two studies have previously reported an association between eosinophilic fasciitis and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, and there is growing evidence that, in addition to reducing atherogenesis and cardiovascular morbidity, these inhibitors may have immunomodulatory properties. They reduce the production of proinflammatory type 1 helper T (Th1) cells and induce differentiation towards Th2 cells. For this reason, HMG-CoA reductase inhibitors might trigger or exacerbate certain autoimmune diseases such as myasthenia gravis, dermatomyositis, polyarthritis, lupus-like syndrome, and lichen planus pemphigoides. They might also, however, be useful for treating other autoimmune diseases and preventing graft rejection in patients who have undergone transplants.

References

Alcohol Intolerance With Facial Flushing Due to Topical Pimecrolimus Treatment

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To the Editor:

Episodic or transient erythema (flushing) is a condition that consists of episodes of sudden reddening of skin on the face, neck, and upper part of the chest or abdomen, that can be accompanied by a sensation of heat or burning as the result of circulatory changes within the skin prompted by a wide variety of triggers. Alcohol is a potent mediator of flushing, mainly through its metabolite acetaldehyde, and this effect can also occasionally be triggered by various drugs, including topical immunomodulators.

We recently observed a case triggered by pimecrolimus—a phenomenon that has been recognized previously, but for which we were unable to find cases described in the literature. The patient was a 54-year-old woman with no relevant history, who had suffered from facial seborrheic dermatitis and sensitive skin. She had been prescribed topical pimecrolimus that had been applied regularly morning and night. Two weeks after treatment began, over the Christmas period, she experienced episodes of more than 30 minutes of intense and marked facial flushing following the ingestion of alcohol. The flushing was not associated with any general symptoms, nor was it accompanied by sweating. The patient had never experienced these symptoms before, she was taking no other treatment, and she had not changed her behavior in any other way, and hence, she established the possible link with the pimecrolimus cream and reported this to her doctors. Although the patient had stopped applying the pimecrolimus a week previously, a challenge test completed with her consent proved positive within 10 minutes (Figure) although the patient said the flushing had been more intense when she had been using the cream. In the follow-up 3 months after suspending the medication, the patient showed no further symptoms.

Flushing can be the exaggeration of a physiological process or a sign of an underlying condition. The erythema is due to increased blood flow that can be due to the direct action of vasodilator substances or changes in the neurologic control of vascularization. Alcohol (ethanol) is rapidly absorbed by the gastrointestinal tract after ingestion. More than 90% is oxidized in the liver into acetaldehyde by alcohol dehydrogenase and then into acetate by aldehyde dehydrogenase. In some individuals of Asian origin intense flushing has been observed even with low doses of alcohol and associated high plasma levels of acetaldehyde. This unusual reaction has been linked to a deficit of an aldehyde dehydrogenase isoenzyme and can be detected through patch testing with ethanol. It has been explained as an increase in plasma levels of acetaldehyde and is possibly triggered by the release of prostaglandins. The ingestion of alcohol with some medicines, fungi, and chemical agents can cause the inhibition of aldehyde dehydrogenase and the accumulation of acetaldehyde, unleashing a clinical condition known as aldehyde syndrome, disulfiram syndrome, or Antabuse syndrome accompanied by a marked cutaneous reaction with flushing.

Local intolerance to topical tacrolimus is common and is observed in 50% of patients. It is generally transient and is different to the uncommon reaction of alcohol intolerance with flushing also described with this medication. This phenomenon has been described in 6% of patients, and a controlled safety study showed this to occur in 7% and 35% of patients treated with 0.1% and 0.03% tacrolimus ointment, respectively. This type of alcohol intolerance has been described in patients treated for atopic dermatitis and in those treated for rosacea, and it has even been described in cases where children have ingested minimal quantities of alcohol in medications containing ethanol.

The mechanism is unknown, although the release of neuropeptides with possible vasodilatory effects in a similar manner to those produced by capsaicin has been implicated. Cyclosporin has similar mechanisms of action and secondary effects, including flushing that has been related to increased levels of prostaglandins and arachidonic acid. Changes in the modulation of aldehyde concentration or dehydrogenase activity have not been reported.

This type of reaction to topical calcineurin inhibitors has been reported with both tacrolimus and pimecrolimus, not surprisingly given their molecular

Figure 1. Flushing affecting the face and neck 10 minutes after a challenge test with ingestion of alcohol.
similarity, which also explains the recently described possibility of cross-reactivity between the 2 substances. It is also possible that the lower absorption of pimecrolimus is responsible for the lower incidence of this secondary effect, as seen with low-concentration tacrolimus.

References


Congenital Self-Limiting Tufted Angioma

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To the Editor:

We report the case of a 1-month-old boy who had had a 5-cm violaceous plaque on the right arm since birth. The plaque was not hot, pulsatile, or painful and had a peau d’orange surface covered with downy hair (Figure 1). The biopsy showed a normal epidermis with dermal vascular proliferation in the form of lobules. The lobules were arranged in a birdshot pattern and were composed of endothelial cells with no signs of atypia or mitosis and with occasional half-moon-shaped peripheral vascular spaces (Figure 2). Immunostaining was negative for glucose transporter-1 (GLUT1). The histologic and immunohistochemical characteristics of the lesion suggested a diagnosis of congenital tufted angioma. The tumor became gradually flatter and had partially disappeared by the time the baby was 1 year old (Figure 3).

Tufted angioma (TA) is a rare benign vascular tumor. Most TAs are acquired and appear during the first year of life or in young people as violaceous macules, plaques, or nodules high on the torso, on the neck, or on the arms.1,2 They may present hyperhidrosis, be painful to the touch, or covered with

Figure 1. Clinical appearance of the lesion at birth.

Figure 2. Histologic appearance of the lesion (hematoxylin–eosin, ×100).
The microscopic appearance of TA is characteristic and shows multiple cell lobules in the middle and lower dermis and in the subcutaneous tissue. The lobules are composed of endothelial cell aggregates arranged in a spiral pattern around the vascular pedicles. When these lobules protrude into the surrounding vascular walls, they take on a half-moon shape, characteristic of TA. Immunostaining is negative for GLUT1, unlike in infantile hemangiomas.

The history of KHE is similar to that of TA as the cells are also organized in capillary lobules (though they are larger, deeper, less circumscribed, and separated by connective tissue). KHE is associated with a greater number of cells, with a higher proportion of fusiform cells. Both diseases show half-moon-shaped capillary spaces around the vascular lobules; the spaces appear to correspond to lymph channels.

Enjolras et al. performed a histologic analysis of vascular lesions compatible with TA or KHE complicated by KMS and found a lymphatic component in most of them. The use of the D2–40 monoclonal antibody, which is a specific marker for lymphatic endothelium, has made it possible to show the presence of lymphatic capillaries in the periphery of the vascular lobules in TA and KHE, though with a different distribution.

TA and KHE share a similar clinical appearance, sometimes share a common complication (KMS), have similar histologic characteristics, and have lymph vessels around the capillaries.

In another study by Enjolras et al., the histologic analysis of vascular tumors complicated by KMS showed findings compatible with KHE during the active phase and more typical of TA thereafter. This set of characteristics common to both tumors supports the idea of a single spectrum of vascular lesions in which the aggressive extreme would be occupied by KHE and the more benign extreme by TA.

A wait-and-see approach in early-onset or congenital cases of TA seems to be the most acceptable course of treatment, as no cases of malignant transformation have been reported. Treatment is considered in cases where vital organs are compromised or symptoms are marked, or to improve the appearance of the patient. The recommended treatment is surgical removal. Systemic corticosteroids, vincristine, or other alternatives may be used, though with highly variable results.

A review by Ishikawa et al. found that treatment of adult TA tended to be applied at an early stage, thus making it difficult to obtain information on the course of the primary lesion and on whether there is a tendency to spontaneously remit.

We present the case of a congenital TA—a rare form that appears to have a greater tendency toward spontaneous remission than later-onset forms. For this reason, we recommend a wait-and-see approach in cases of early-onset TA or TA present at birth.

References

Letters to the Editor

Staphylococcus aureus Sepsis as a Complication of Scabies

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To the Editor:

Scabies is a parasitosis considered to be a public health problem especially in developing regions of the world. Local and systemic secondary infections and other complications like acute poststreptococcal glomerulonephritis are major causes of morbidity in this type of patient.1

A 2-month-old infant was admitted to hospital with a diagnosis of scabies and fever, and treatment with permethrin cream, 5%, was prescribed. The day before admission the infant developed a hot, erythematous, edematous plaque below the left knee (Figure 1). Two days later he was transferred to the pediatric intensive care unit with increased signs of respiratory distress. A further chest x-ray revealed empyema and hemothorax in the left lung that required drainage of 35 cm³ of yellowish fluid with a pH of 6.86. The abscess on the knee was also drained (Figure 2). Blood cultures and cultures from the skin lesion and the empyema were positive for Staphylococcus aureus. The prescribed antibiotics were replaced with intravenous cloxacillin (25 mg/kg/d) for 14 days, and a favorable response was seen in the patient.

Scabies is an infestation caused by the hominis variant of the Sarcoptes scabiei mite, a human parasite that tunnels under the epidermis. It affects both sexes and all age groups equally. There are more than 300 million new cases each year all over the world.2 Scabies is a highly contagious disease that is generally transmitted by direct human contact, although cases have been described in which transmission occurred through contact with fomites and contaminated animals.

Secondary bacterial infections can sometimes occur in skin lesions and cause local and, less commonly, systemic complications.3,4 A study by Itzhak Brook3 analyzed the bacterial flora found in lesions with secondary infections and found the most common aerobe was S. aureus, while the most common anaerobes were Peptostreptococcus species.

Figure 1. Hot erythematous and edematous plaque on the leg.

Figure 2. Drainage of purulent material from the abscess on the knee.
Secondary infection with *Streptococcus pyogenes* can trigger acute poststreptococcal glomerulonephritis and rheumatic fever.\(^5\)\(^6\)

The exact pathogenic mechanism associated with the organisms isolated in skin lesions with secondary infection has not yet been determined. In our case, the pathogenic role of *S aureus* was clear, as it was isolated in the blood, the pleural fluid, and the skin lesion. Thus the parasite entered the epidermis through a break in the skin leading to bacteremia and the consequent empyema.

Early diagnosis of scabies is essential in order to initiate appropriate treatment with a scabicide. Similarly, secondary bacterial infection must be managed through local or, occasionally, systemic antibiotics, and pus must be drained from abscesses\(^3\) in order to avoid complications that could potentially endanger the life of the patient.

**References**


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**Eruptive Xanthomas After Onset of Diabetes Mellitus**

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**To the Editor:**

We recently treated a 33-year-old man who was admitted to our hospital with abdominal pain accompanied by nausea, vomiting, and hyperglycemia that had begun 4 days earlier and reflected the onset of diabetes mellitus. The patient had a history of hypertension diagnosed in the last 3 months, predominantly abdominal obesity, with a body mass index of 31.5 kg/m\(^2\), severe alcoholism, and hypercholesterolemia diagnosed a year ago. He was receiving dietary treatment. The patient’s father had type 2 diabetes mellitus that began in his thirties.

The patient reported polyuria, polydipsia, and polyphagia for the last 3 weeks, along with weight loss of 10 kg. Around that time, he began to develop erythematous papules of 1 to 4 mm in diameter on his back, and these turned yellow within a few days. Some of the lesions had a peripheral halo and were accompanied by mild pruritus. The lesions were initially distributed on the back but later spread to the arms and legs, buttocks, and in particular, the sacral region (Figure 1).

Laboratory analysis during admission revealed the following: glucose, 257 mg/dL; total cholesterol, 418 mg/dL; triglycerides, 853 mg/dL; high-density lipoprotein cholesterol, 32 mg/dL; low-density lipoprotein cholesterol, 218 mg/dL; direct bilirubin, 0.1 mg/gL; indirect bilirubin, 6.1 mg/dL; aspartate aminotransferase, 18 mU/mL; alanine aminotransferase, 20 mU/mL; \(\gamma\)-glutamyltransferase, 66 mU/mL; lactate dehydrogenase, 398 mU/mL; and alkaline phosphatase, 230 mU/mL. Gasometric analysis of venous blood revealed slight metabolic acidosis. Thyroid function, insulinemia, and C-peptide concentrations were within normal ranges and analysis of anti-islet cell antibodies was negative.

Abdominal ultrasound revealed diffuse hepatic steatosis with hepatomegaly. Histology of the skin lesions (Figure 2) revealed infiltration of the superficial and middle dermis by uniform polygonal mononuclear macrophages with a foamy cytoplasm, with a tendency toward perivascular aggregation and without accompanying

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**Figure 1.** Multiple yellow papules with a peripheral erythematous halo on the back of the arm and the back.

**Figure 2.** Macrophages loaded with intracellular lipids (foam cells) (hematoxylin-eosin, \(\times400\)).
lymphocytes. There were no notable changes in the epidermis.

Following stabilization of the patient, treatment was initiated with a diabetic diet, insulin therapy, fenofibrate 160 mg/d in slow-release tablets, and metformin 850 mg every 12 hours.

A month and a half later, after the patient had lost weight, done regular physical exercise, and received medical treatment, the lesions had remitted, though some had left residual hypertrophic scars. Blood glucose and triglycerides had returned to almost normal levels (glucose, 111 mg/dL; triglycerides, 163 mg/dL).

Eruptive xanthomas are yellow or orange papules measuring only a few millimeters in diameter and generally with an inflamed base. They are distributed on the thighs, legs, and extensor surfaces the extremities. They can display a Koebner phenomenon and are sometimes accompanied by pruritus and pain. The lesions usually remit within weeks and can heal leaving behind residual keloid scars. Foamy macrophages are observed by histology, accompanying a variable mixed infiltrate of lymphocytes and neutrophils.

The lesions can occur in the context of hyperchylomicronemia or hypertriglyceridemia as a result of abnormalities in lipid metabolism, producing intracellular and extracellular lipid deposits. Most cases occur as a result of deficient lipoprotein lipase activity. This lack of lipoprotein lipase function occurs in situations of primary lipoprotein lipase deficiency (apoprotein CII abnormality, such as Frederickson type-I hyperlipoproteinemia) or secondary to reduced insulin activity (eg, diabetic dyslipidemia) or hepatic overproduction of chylomicrons (Frederickson type-4 hyperlipoproteinemia or endogenous familial hypertriglyceridemia).

The hypertriglyceridemia associated with diabetes occurs via a dual mechanism. Firstly, there is a reduction in chylomicron clearance that leads to an increase in very low-density lipoproteins and, consequently, to hypertriglyceridemia. Secondly, lipoprotein lipase requires minimum levels of functional insulin in peripheral blood, and lack of insulin activity or insulin resistance lead to acquired lipoprotein lipase deficiency. For that reason, some authors have proposed the term diabetic dyslipidemia.

Diabetes is one of the most common causes of secondary hypertriglyceridemia. Other common causes include liver cirrhosis, hypothyroidism, and pancreatitis. Eruptive xanthoma has been described less often in cases of hypothyroidism, nephrotic syndrome, von Gierke disease, excessive alcohol consumption, chronic cholestasis, treatment with systemic corticosteroids, estrogens, or retinoids, and generally with any processes that involve hyperlipidemia, whatever the underlying mechanism.

Differential diagnosis should include disseminated, tendinous, and tuberous xanthoma, eruptive histiocyteoma, granuloma annulare, juvenile xanthogranuloma, molluscum contagiosum, and necrobiotic xanthogranuloma. Hypertriglyceridemia should always be ruled out in cases of eruptive xanthoma, along with the possible association with diabetes mellitus, because eruptive xanthoma can sometimes form part of the initial presentation of the disease, as in our case. Even with a presumptive diagnosis of eruptive xanthoma, biopsy is advisable, since cases of histiocytosis can appear similar.

Adequate treatment requires rigorous control of the underlying hyperlipidemia. This requires a diet low in fats and rapidly absorbed carbohydrates, as well as reduction of weight and regular physical exercise, particularly in patients with insulin resistance.

In summary, eruptive xanthomas may be associated with diabetic dyslipidemia, not just with hypertriglyceridemia, and with a complete accompanying metabolic syndrome that may require urgent medical treatment.

References
