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photo quiz

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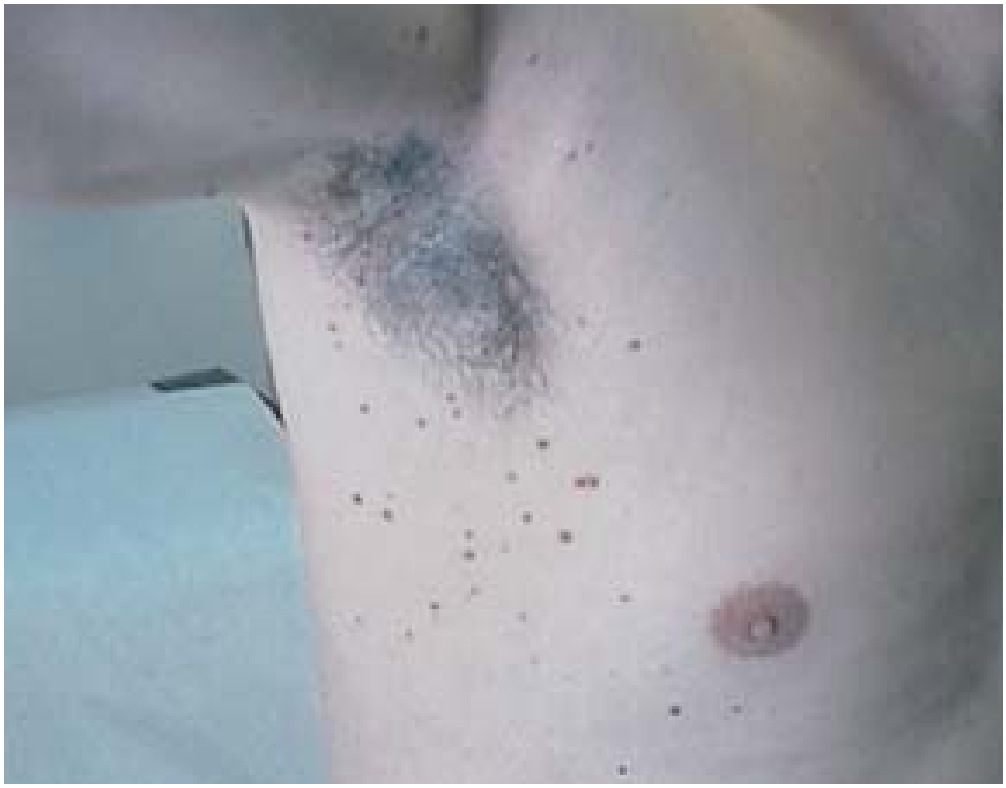
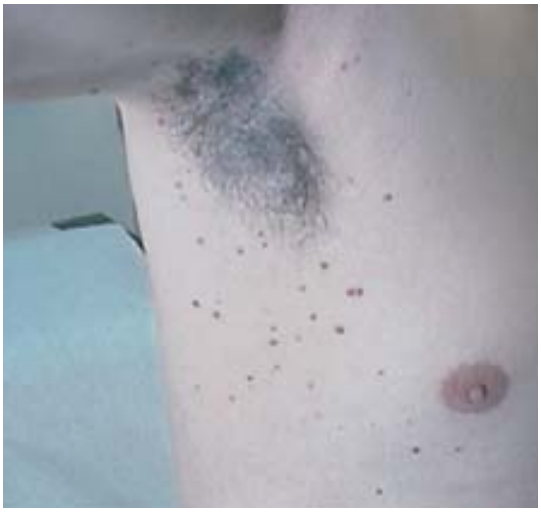


A 35-year-old firefighter presents with yellow-red papules symmetrically located in the inguinal and axillary area.

What is your diagnosis?

PLEASE TURN TO PAGE 377 FOR DISCUSSION

The Diagnosis



DISCUSSION

Non-Langerhans cell histiocytoses, or non-X-histiocytoses, belong to the category of class II histiocytoses. By definition, this group compromises non-malignant diseases characterized by a proliferation of mononuclear phagocytic histiocytic cells that lack Birbeck granules and are S-100 and CD1a-negative, yet positive for a variety of macrophage markers. Included in this category are juvenile xanthogranuloma, generalized eruptive histiocytosis, xanthoma disseminatum, benign cephalic histiocytosis, sinus histiocytosis with massive lymphadenopathy, reticulohistiocytoma cutis, papular xanthoma, necrobiotic xanthogranuloma, and Erdheim-Chester disease. In general, these disorders have unremarkable lipid profiles and may be associated with paraproteinemias and lymphoproliferative disease.

Xanthoma disseminatum (XD), also known as Montgomery's syndrome, is a rare, benign, non-inherited, normolipemic, mucocutaneous, non-Langerhans cell histiocytosis. This condition was initially described by Montgomery and Osterberg[1,2] in 1938. XD predominantly affects male children and young adults (2:1 male:female) with approximately 60% of patients being affected by the age of 25.[3] Aside from mucocutaneous involvement, the disorder may also manifest itself in several internal organs including the meninges, liver, spleen, and bone.

The initial cutaneous presentation of XD is an eruption of many red-brown papules scattered over the face, neck, trunk, and proximal extremities, with a predilection for flexural areas including the antecubital and popliteal fossae. Gradually, as the lesions turn yellowish they may become confluent (especially in the flexures and intertriginous sites), eventually forming verrucous xanthomatous plaques. Skin lesions may resolve spontaneously after several years. Our patient had flexural and mucosal involvement but no laryngeal involvement or diabetes insipidus.

Mucosal and visceral involvement are characteristic of XD. Approximately 40 to 50% of patients develop mucosal disease, especially involving the oral, nasopharyngeal, respiratory, anal, or conjunctival membranes.[3] When present in the respiratory tract, the xanthomatous deposits can produce dysphagia and dyspnea. At least five cases have been reported in which tracheostomy was required to relieve respiratory distress.[15]

Meningeal involvement is also common, with approximately 50% of patients developing a xanthomatous infiltration of the floor of the third ventricle and infundibulum, leading to hypothalamic-pituitary axis involvement and secondary diabetes insipidus.[3,4] When this occurs, the associated polydipsia and polyuria are typically mild and transitory, resolving as cutaneous lesions remit. Less common neurologic findings include exophthalmus, blindness, cerebellar ataxia, and internal hydrocephalus.[6] In addition, there has been a case of peripheral neuropathy associated with loss of tendon reflexes and sensory, vibratory, and proprioceptive impairment secondary to progressive XD.

Progressive bone involvement in XD has been reported, although only rarely. Osteolytic lesions, especially of the long bones, shoulder, pelvis, wrist, and phalanges, have been seen.[11] Elevation in alkaline phosphatase and the calcium:phosphate ratio have not been observed. Although rare, XD involving the myocardium, bowel, skeletal muscles, gallbladder, kidney, stomach, ovaries, lymph nodes, pancreas, uterus, and adrenal glands has been noted during autopsy examinations.[3,8] There has been a reported association with Waldenström's macroglobu-

linemia,[12] as well as hepatobiliary disease.[6] Because XD usually has a good prognosis and is self-limited, visceral involvement in most cases probably does not cause organ dysfunction, thus often remaining undiagnosed.

The pathogenesis of XD is unclear but appears to be caused by local accumulation of lipid due to a granulomatous histiocytic process induced by an unknown stimulus.[3] However, unlike other xanthomatous diseases, there is a lack of lipid metabolism of transport abnormalities in XD. In the earliest XD lesions, a scalloped histiocyte is present.[13] Histopathologic examination of more mature lesions demonstrates a dermal infiltrate consisting of a mixture of histiocytes, foamy (xanthoma) cells, inflammatory cells, and Touton giant cells. In some instances, only foam cells are present. On occasion siderosis my be seen. Immunochemistry demonstrates S-100 and CD1a negativity. There is a positive expression of monoclonal and polyclonal monocyte/macrophage antigens, CD68 (KP1), CD11b, CD11c, CD14, lysozyme (variable), MAC-387 (variable) and alpha-1-antitrypsin (variable), and dermal dendrocyte antigen factor XIIIa.[8,13,16]

Ultrastructurally there is an absence of Birbeck granules; however, myeloid bodies and membrane-bound fat droplets are present.

Although overlap exists, three prognostic clinical scenerios of XD have been described: 1) persistent (most common and most stable); 2) self-healing (rare); and 3) progressive with organ dysfunction (rare).[9] Treatment of XD is symptomatic, and no uniformly effective therapy is available. Multiple therapeutic regimens have been utilized including systemic cortiocosteroids, lipid-lowering agents, Vinca alkaloids, alkalating agents, azathioprine, cyclophosphamide, methotrexate, chlorambucil, intralesional gamma-interferon, antimalarials, and radiation; however, all inconsistently affect clinical course and outcome. Vasopressin injections have been used to treat accompanying diabetes insipidus. Cosmetically disfiguring or obstructing lesions have been treated with cryotherapy, dermabrasion, electrocautery, and surgery. In general, XD is considered a chronic disease with a relatively benign course and favorable prognosis. However, because of the potential for organ involvement mucosal complications, and disfigurement, long-term follow-up for patients is warranted.

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