Case Report

Intralymphatic Histiocytosis and Hypertrichosis Occurring Over the Site of a Titanium Hip Implant in a Patch Test Negative Patient

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Intralymphatic histiocytosis typically presents as erythematous indurated plaques on the limbs of older individuals. Some affected individuals have underlying rheumatoid arthritis. When intralymphatic histiocytosis is associated with joint replacement surgery, plaques commonly occur near the skin incision. Biopsy reveals dilated lymphatics filled with large numbers of histiocytes. Although the etiology of this peculiar phenomenon is unknown, numerous cases have been associated with metal implants. We report an additional patient with intravascular histiocytosis associated with a metal hip implant. Patch testing to a special metal series which included the component of the implant was negative. Our patient also developed hypertrichosis with silvery hairs overlying her plaque. We review the literature on intralymphatic histiocytosis associated with metal implants, present the diagnostic histologic findings, and explore possible etiologies for this uncommon reactive phenomenon.
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Key Words: *Intralymphatic histiocytosis, hip implant, metal, patch test*

INTRODUCTION

Intralymphatic histiocytosis is defined by the presence of numerous macrophages filling dilated lymphatics. The disorder was first described in 1994 by O'Grady et al under the name of intravascular histiocytosis.[1] Further studies identified the lymphatic origin of the vessels by staining with the immunohistochemical marker D2-40,[2] and led to intralymphatic histiocytosis becoming the favored name for this uncommon condition.[3,4] The disorder is most often associated with underlying inflammatory disorders. Most cases have been associated with rheumatoid arthritis but diabetes, Merkel cell carcinoma, Crohn's disease, infection, lupus anticoagulant and reaction to metal implants have all been associated with this reaction pattern.[4] Intravascular histiocytosis is more common in women than in men,[3,4] and lesions are often noted near joints. The skin changes that accompany this disorder may mimic cellulitis and are typically described as erythematous and indurated plaques. The extent of the cutaneous involvement does not typically correlate with the severity of the patient's underlying condition. Plaques occurring overlying surgical scars following joint replacement may occur months to years after surgery.[3] Lymphostasis is thought to be an important factor.[2] Some authors suggested that intralymphatic histiocytosis be separated into primary and secondary forms, because some cases appear to occur in isolation in an idiopathic manner.[4] Angioendotheliomatosis as well as intravascular thrombi can be associated with some cases. We describe an additional patient who developed intralymphatic histiocytosis in association with a titanium implant.

CASE PRESENTATION

An 86 year old woman presented for evaluation of tender erythematous plaques on her left thigh and buttocks. She had undergone left hip replacement surgery 1 ½ years previously with a titanium implant (Summit Tapered Hip System by DePuy). The titanium implant included a porous coating (Porocoat) that was part of a "cementless" method. She described a coin-shaped area of erythema over the hip near the inferior aspect of her surgical scar that had begun approximately one year after her hip replacement surgery and then gradually enlarged. Treatment with courses of oral cephalexin and then clindamycin for presumed cellulitis was ineffective. Her medical history was remarkable for nickel allergy, hypertension, carpal tunnel syndrome, spinal stenosis, celiac disease, and a history of a cerebral vascular accident in the past. She had undergone right hip replacement 4-1/2 years ago. Her medications included atenolol, diazepam, hydralazine, lisinopril, acetaminophen and hydrocodone, and amlodipine besylate. She had no history of rheumatoid arthritis. Examination revealed a 12 x 8 cm erythematous plaque. Hypertrichosis was noted overlying the areas of erythema (**Figure 1** and **2**). Biopsy revealed dilated lymphatics filled with large numbers of histioytes (**Figure 3** and **4**). We performed patch testing to our special metal series which includes: aluminum hydroxide 10%, copper sulfate hexahydrate 1%, ammoniated mercury 1%, palladium chloride 1%, tin chloride 0.5%, amalgam [Hg 2.5%, Ag 1.7%,

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Cu 0.3%, Sn 0.4%, Zn 0.025%] , vanadium pentoxide 10%, titanium oxide 0.1%, molybdenum (V) chloride 0.5% (all obtained from AllergEAZE Corp). Patch testing to all these metals was negative. Treatment with clobetasol ointment was associated with marked improvement in the plaque. The plaque resolved after about one year, and has remained clear for more than one year. Her hypertrichosis resolved along with the other skin changes.

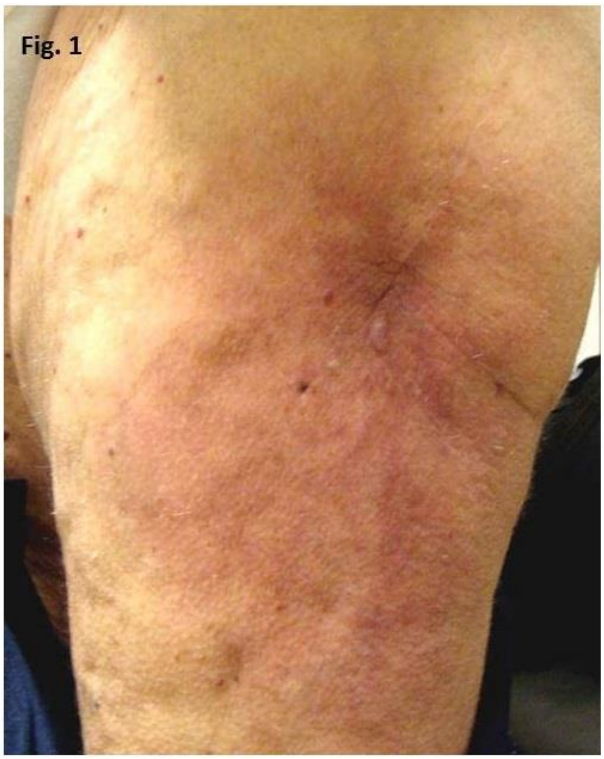

Figure 1. The left thigh reveals a poorly circumscribed erythematous and indurated plaque that mimics cellulitis.

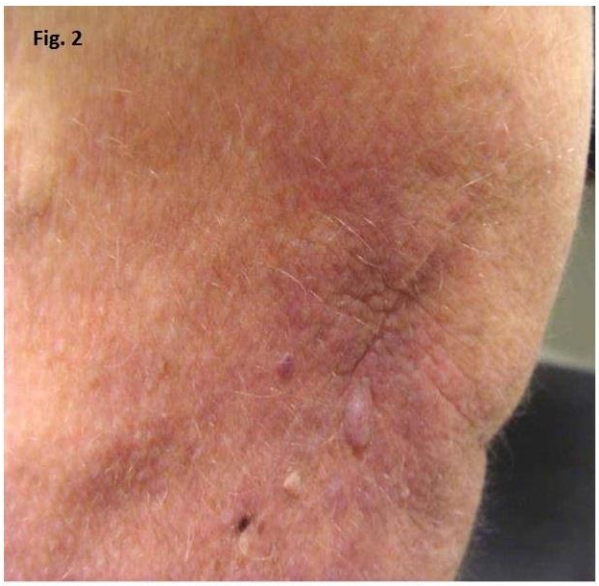

Figure 2. Close up the left thigh reveals an increased number of silvery hairs within the erythematous patch.

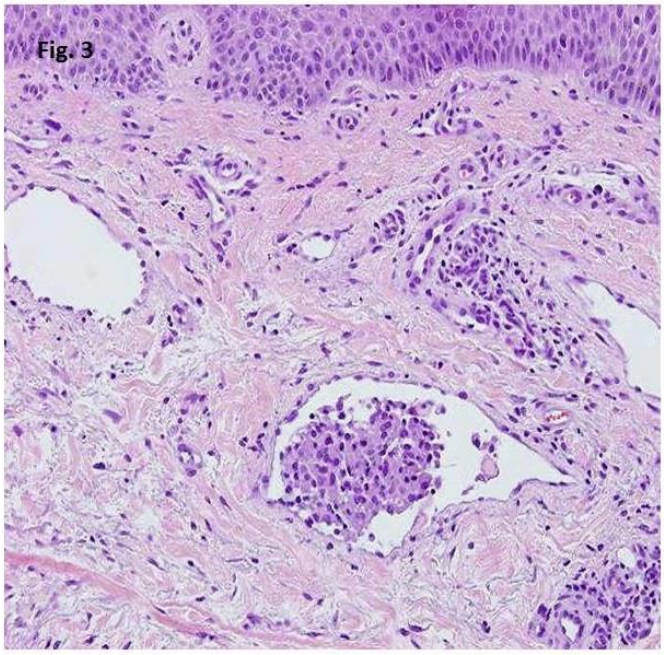

Figure 3. Biopsy reveals markedly dilated lymphatics, some of which are filled with large numbers of histiocytes. The epidermis fails to show changes typical of contact dermatitis. (Hemotoxylin and eosin stained sections; original magnification 100x).

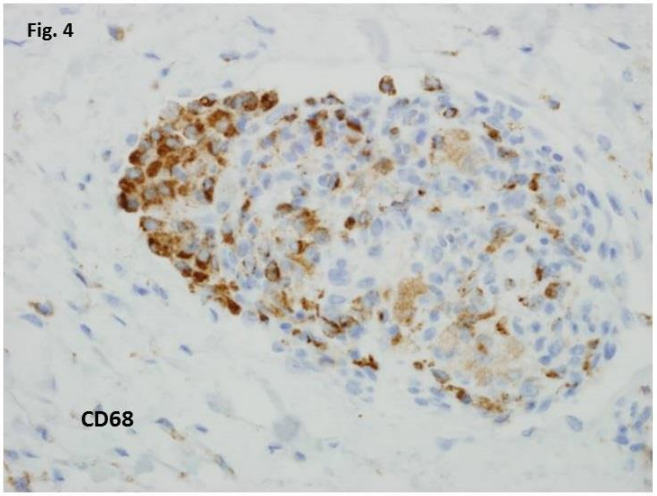

Figure 4. Immunohistochemical staining for CD68 confirms that the collection of cells within the dilated lympatics are histiocytes (original magnification 200x).

DISCUSSION

Since it was first described 20 years ago, the number of cases of intralymphatic histiocytosis reported has been steadily increasing.[1-31] Although the types of conditions associated with this phenomenon have also increased, rheumatoid arthritis and joint replacement surgery with metal implants remain predominant underlying conditions associated with this phenomenon.[3,4,13] The course of intralymphatic histiocytosis varies and does not parallel the underlying disease.[6] Chronic inflammation and vascular changes seem to be important in the pathogenesis. Lymphatics are markedly dilated and filled with large numbers of histiocytes. Vascular

proliferation may be noted, but features such as nuclear atypia or abnormal mitotic figures are note encountered. There may be difficulty in establishing a histologic diagnosis when pathologists are not familiar with the characteristic histologic findings. Some cases reported as reactive angioendotheliomatosis likely represent intralymphatic histiocytosis.[5,20,29] Lymphatic stasis secondary to chronic inflammation is suspected as an important inciting factor.[3] The presence of intralymphatic histiocytosis in an area that had been treated with left axillary lymphadenectomy fortifies the hypothesis that lymphatic stasis may be important.[17,18] Less common associations include concurrent carcinoma, melanoma, lymphedema, and even the Klipel-Trenauny Weber Syndrome.[3,4,6-12] Metal implants have been increasingly recognized as an important association (**Table 1**).[3,12-16] Our patient's implant consisted of titanium, and we considered the possibility that metal sensitivity might be a contributing factor to the pathogenesis of intralymphatic histiocytosis. Patch testing in our patient failed to identify a relevant metal contact allergy. We share the suspicion that a localized "immunocompromised district" likely accounts for the changes that give rise to intralymphatic histiocytosis.[34] Joint replacement can be associated with a variety of unusual localized reactions. A patient who had undergone a polyethylene based right total knee prosthesis was noted to have intracellular polarizable material within soft tissue mass adjacent to the tibial prosthetic insert.[32] This change as well as the presence of molybdenum in the soft tissue of lesions may be explained by chronic inflammation.[12] Chronic inflammation is also known to be a cause of hypertrichosis and likely accounts for the hypertrichosis noted overlying our patient's plaque.[33] Our patient's hypertrichosis resolved along with her plaque. The degree of localized chronic inflammation may prove to be important in deciding who develops this unusual reaction pattern. The overlapping histologic features noted in intralymphatic histiocytosis and reactive angioendotheliomatosis[20,29] also can be explained by chronic localized inflammation. In retrospect, some cases might be classified differently today.[22] Oral lesions[34] and intralymphatic histiocytosis occurring in the setting of a warty growth[35] seem to support the hypothesis that lesions can occur anywhere there is chronic localized inflammation. Treatment is difficult. Some patients with underlying arthritis have noted improvement with joint replacement surgery. Although in other individuals joint replacement surgery has been the triggering factor. Topical and systemic corticosteroids may be of benefit. Although skin tape was thought to lead to improvement,[10] intralymphatic histiocytosis has a variable course that makes evaluation of therapeutic options difficult. Infliximab may be of value for extensive lesions.[8] Topical tacrolimus 0.1% ointment has been noted to be helpful for localized lesions.[35]

Table 1. Reported Cases of Intralymphatic Histiocytosis Associated with Metal Implants.

Grekin S et al (13)	72 year old man	3 years after metal implant to stabilize fractured humerus
Watanabe T et al (12)	75 year old man	Left knee metal implant containing manganese and molybdenum. Molybdenum noted in tissue by x-ray spectroscopy.
Requena L et al (3)	63 year old man	Right hip metal prosthesis for joint replacement
	65 year old	Right hip metal prosthesis for joint replacement
Rossari S et al (14)	71 year old man	Left and right knee metal joint replacements 1 year previously
De Unamuno B et al (16)	74 year old woman	2 weeks after right shoulder metal implant for humerus fracture
Saggar S et al (15)	78 year old woman	15 years after right hip replacement with a metal prosthesis. Had bilateral knee replacements 3 and 6 years previously
Present case	86 year old woman	1-1/2 years after left hip replacement. Had right hip replacement with a metal implant 4-1/2 years previously.

CONCLUSION

Clinicians should be aware of intralymphatic histiocytosis so that an accurate and timely diagnosis can be made. Our case suggests that contact sensitivity to metal components is unlikely to be a contributing factor in metal implant associated cases. Evidence suggests that localized chronic inflammation and a localized "immunocompromised district" are likely causative.

CONFLICT OF INTEREST

There was no funding for this project. We have no conflict of interest with the material presented.

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