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## Case Report

### Generalized eruptive histiocytosis associated with a novel fusion in LMNA-NTRK1

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## Abstract

Non-Langerhans cell histiocytosis (NLCH) is a histiocyte disorder comprised of dermal dendritic histiocytes with a characteristic staining pattern. Erdheim-Chester disease (ECD) is a subset of NLCH in which patients experience bone pain with corresponding changes on imaging. In addition, these patients show other evidence of systemic involvement, which can also be identified with imaging. This disease can occasionally present with cutaneous findings. We present a case of generalized eruptive histiocytosis (GEH), misdiagnosed as ECD, found to have an NTRK1 gene rearrangement. This is the first report of an NTRK1 kinase fusion with NLCH. The implication is unclear and further studies are warranted.

**Keywords:** Non-Langerhans Cell Histiocytosis, Histiocytosis, Erdheim-Chester, NTRK1, LMNA

## Introduction

Histiocyte disorders are conventionally divided into Langerhans Cell Histiocytosis (LCH) and Non-Langerhans cell histiocytosis (NLCH). NLCH are composed of histiocytes derived from a dermal dendritic cell lineage. Included in this category are benign cephalic histiocytosis, xanthogranuloma, multicentric reticulohistiocytosis, necrobiotic xanthogranuloma, generalized eruptive histiocytosis (GEH), Erdheim-Chester disease (ECD), and xanthoma disseminatum [1]. As opposed to Langerhans cells, which stain positive for CD1a and S-100, the cells of NLCH characteristically stain for CD68, factor XIIIa, and show lack of Birbeck granules on electron microscopy [1]. Notably, there are exceptions to this staining pattern in both Rosai-Dorfman disease and indeterminate cell histiocytosis [1].

Erdheim-Chester disease (ECD) is a rare form of systemic NLCH that may sometimes develop cutaneous xanthoma-like lesions. Usually, this condition is characterized by bone pain with sclerotic lesions showing tracer uptake via <sup>99</sup>Tc bone scintigraphy [2], in addition to an irregular kidney border producing a “hairy kidney” on CT scan in about half of the cases [2,3]. Treatment includes interferon alpha and BRAF inhibitors in appropriate patients [2], as well as corticosteroids, radiotherapy, and even chemotherapy [4].

Generalized eruptive histiocytosis (GEH) is a benign condition, the features of which were first described by Winkelmann & Müller described in 1963. It is characterized by symmetric crops of skin-colored or blue papules on the trunk and extremities without a tendency to coalesce [5].

The NTRK1 gene encodes for a tyrosine kinase receptor, which regulates cellular proliferation during nervous system development [6]. Activation results in promotion of multiple signaling pathways, including MAPK and NFκB [7].

We present a case of GEH, misdiagnosed as ECD, which responded to PUVA after failing treatment with multiple systemic agents. Interestingly, the lesional tissue harbored a genetic rearrangement resulting in a LMNA-NTRK1 fusion protein, which has not been previously reported.

## Case synopsis

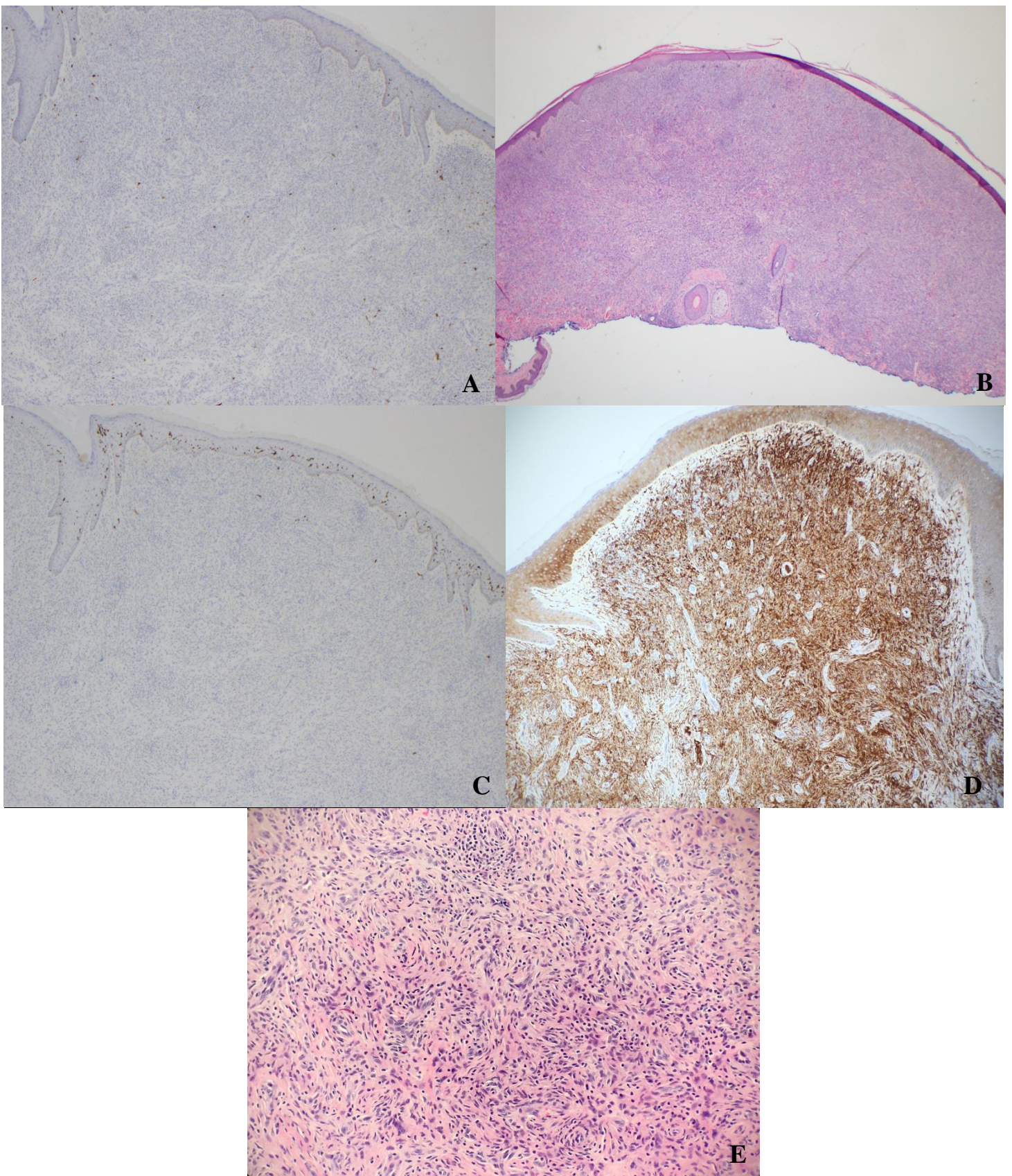
The patient is a 28 year-old, healthy, man with no significant past medical history who initially noticed hyperpigmented macules on his face 5 years prior to presentation. Over the following 3-4 years, the lesions became more papular and progressed to involve the trunk and extremities. They became slightly pruritic, but were otherwise asymptomatic. He lacked other systemic symptoms, including vision changes, headaches, or increased urination. He was treated with topical steroids without improvement. Upon his initial visit to our institution, his exam was notable for diffuse and somewhat symmetric firm, brown and red papules and plaques ranging in size from 2-15 mm on the face, trunk, and extremities (Figure 1).



**Figure 1.** Patient's back on initial presentation. There are discrete brown and skin colored firm papules.

The oral mucosa was clear. There was no lymphadenopathy. Three biopsies were performed on the left arm and flank, all of which confirmed a diagnosis of NLCH. Immunohistochemical stains were positive for factor XIIIa and CD 68, and were negative for S-100, CD 1a, and CD 34 (Figure 2a-e). Next-generation sequencing (NGS) through FoundationOne™ showed an unreported rearrangement resulting in a fusion between neurotrophic tyrosine kinase receptor, type 1 (NTRK1) and lamin A (LMNA). No other mutations were identified.





**(Figure 2A-E).** a) Photomicrograph. Medium power Hematoxylin and Eosin. The epidermis is unremarkable. There is a nodular and diffuse histiocytic infiltrate in the dermis. b) Photomicrograph. High power Hematoxylin and Eosin of the histiocytic infiltrate. c) Photomicrograph. S-100 immunostain shows negative staining of the infiltrate. d) Photomicrograph. CD1a immunostain shows negative staining of the infiltrate with normal internal controls. e) Photomicrograph. CD163 immunostain shows diffusely positive staining of the infiltrate.

The patient's presentation was also notable for joint pains in the knees, wrists, and ankles. This was thought to be related to vigorous physical activity, but based on these symptoms he was given the presumptive diagnosis of Erdheim-Chester disease by another specialty department. Work-up included full body PET/CT scans, brain, T-spine, and L-spine MRI, bone scan, bone marrow biopsy, and bone marrow flow cytometry, all of which were unremarkable.



After presentation, he was treated with imatinib 400 mg daily off-protocol for a month with no response in the joint pains and progression of cutaneous involvement. He was then transitioned to interferon alpha 2b, 3 million units, 3 times weekly for 5 months without improvement, so anakinra was added. There was no improvement after 1 month of combined treatment, so all therapy was stopped. Five months later, he was started on systemic PUVA, and after 31 treatments, his lesions had notably faded (Figure 3).



**Figure 3.** Clearing of the lesions on the patient's back after 31 treatments with PUVA, working up to 13J, 10 min 3x weekly.

## Discussion

This patient was initially diagnosed with ECD given his arthralgias in conjunction with NLCH on skin biopsy. However, we propose that his disease was misdiagnosed given a lack of evidence of systemic involvement on imaging and bone marrow cytologic studies. He more likely represents a case of GEH. The joint pains in this patient were possibly related to vigorous physical activity, and eventually subsided with non-steroidal anti-inflammatory medications, in addition to PUVA and a less enthusiastic exercise regimen. Although xanthoma disseminatum may also present with wide-spread cutaneous lesions, this condition usually affects the flexural areas and tends to coalesce into larger plaques and nodules [1].

Winkelman & Müller first described the criteria for GEH in 1963 [5]: (i) widespread, essentially symmetric, multiple lesions, particularly involving the trunk and proximal limbs and, rarely, the mucous membranes; (ii) distinct flesh-colored to blue-red papules without a tendency to group; (iii) progressive development of new crops of lesions for years, without antecedent history of trauma; (iv) spontaneous resolution of lesions towards brown macules or complete disappearance; (v) a benign histological picture of mononuclear histiocytic cells.

Interestingly, during our patient's work-up, a tumor sample was sent to FoundationOne™ for NGS, which identifies genomic alterations within hundreds of cancer-related genes. He was found to have a genetic mutation in NKRT1, resulting in fusion between the N-terminal portion of LMNA (Lamin A, possibly exons 1-5) and the C-terminus of NTRK1 (possibly exons 11-17). NKRT1 plays a major role in peripheral and central neuronal development [6]. This gene encodes a tyrosine kinase receptor, which activates multiple downstream pathways, including MAPK and NFκB [7]. NKRT1 gene mutations have not only been reported in conditions characterized by neural dysfunction [8], but also in lung and thyroid carcinoma [9,10] and spitzoid neoplasms [11]. There is also one prior case reporting a fusion of LMNA-NTRK1 in a patient with soft tissue sarcoma metastatic to the lung [12]. In that case, a fusion between exons 1-2 of the lamin A/C gene and exons 11-17 of the NTRK1 gene were found by FoundationOne™ NGS. After failure of chemotherapy and other targeted therapies, the patient was enrolled in a stage I clinical trial with the selective TRK inhibitor, LOXO-101. This resulted in tumor regression and relief of tumor-associated clinical symptoms [12]. It is possible that our patient would respond to a TRK1 inhibitor given the similar fusion protein.

Treatment of GEH is not well-documented, likely because it is both rare and thought to be a self-limited condition. There have been reports of successful clearance with isotretinoin and PUVA, among others [13,14]. In our patient, no lesions were noted to regress spontaneously prior to initiation of PUVA.

Once a diagnosis of GEH is suspected, patients should undergo a thorough work-up, including blood tests, imaging, and perhaps a bone marrow biopsy, to rule out systemic involvement. If needed, a referral should be made to hematology/oncology to discuss the need for chemotherapy or other systemic treatments, including corticosteroids, chemotherapy, radiotherapy, interferon alpha,

and BRAF inhibitors [2,4]. After isolated cutaneous involvement has been confirmed, localized treatment should commence if desired by the patient. Since this condition is generally thought to be benign and self-limited, a watchful waiting strategy may also be appropriate.

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