Disfiguring Nodular Cephalic Xanthoma Disseminatum: An Exceptional Variant of a Forgotten Entity

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SHORT COMMUNICATION

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Xanthoma disseminatum (XD) is an extremely rare cutaneous, normolipidemic, proliferative disorder of the Mononuclear Phagocyte System. It was first described by Von Gräfe and Virchow but recognized as a distinct entity by Montgomery & Osterberg in 1938 (1). Approximately 140 cases are reported in the English literature. Clinically, XD is characterized by a symmetrical skin eruption of reddish papules or nodules, with predilection for the head, neck, flexural and intertriginous areas. These lesions, initially isolated, tend to slowly merge into large yellowish plaques, during years. The mean age at presentation is 30 years and male cases outnumber female ones by a ratio of 2:1. XD is generally thought to be a benign disorder with a chronic progressive course (2–4). Caputo et al. (5) recognized 3 clinical variants of XD: 1) a self-healing form; 2) a persistent form and 3) a progressive multi-system (MS) form. The report rate of this entity is becoming even lower now than in past years, perhaps due to its high diagnostic overlap with Erdheim-Chester Disease (ECD) (6, 7).

CASE REPORT

We hereby describe the case of a previously healthy 47-year-old Caucasian woman presented to our attention in January 2011, with a 2-year long history of cephalic xanthomas. Her lesions consisted of yellow periorcular and perioral plaques extending to the zygomatic area as well as small yellow hard-elastic nodules growing next to the inner canthi (Fig. 1). Complete radiological, hematological (blood count, metabolic, renal and liver functions/profiles) and endocrinological examinations all tested negative and failed to reveal any systemic involvement. Five years after our first diagnosis, she suffered of ischemic heart failure and therefore underwent percutaneous revascularization to complete normalization of cardiac function. During the following 7 years, the lesions displayed a slow but progressive extension with symmetrical involvement of the whole face (Fig. 1). She never developed diabetes insipidus or any other signs of systemic involvement. Previous therapy (hydroxychloroquine and cyclophosphamide) and surgeries (including CO2 laser therapy) led to constant recurrences and subsequent regrowth of lesions, together with surgery-related keloid scars, resulting in high mechanical, psychological and sociological impairment. Skin biopsy (Fig. 1) showed a polymorphic dense upper- and mid-dermal infiltration consisting of large histiocytes, admixed with few lymphocytes and neutrophils. Histiocytes were mostly characterized by large nuclei often with prominent nucleoli and an abundant pale cytoplasm. Foamy, Touton and Langhans cells were also present, focally in large numbers. There were no signs of epidermotropism. Immunohistochemical profile of the histiocytes was positive for CD4, CD11c, CD14, CD68/PGM1, CD163, FXIIIa, vimentin, lysozyme, fascin but tested negative for CD1a, CD34 and CD207/langerin. Ki-67 stained 1–5 % of the cells. Altogether, clinical–pathological examination led to a non-conclusive diagnosis of ‘xanthogranuloma’ vs xanthoma disseminatum. BRAFV600E analysis failed to reveal any alteration. Sixteen years after the first manifestation, the patient is alive and in a good clinical condition, although with chronic persistent evolution of the disfiguring lesions.

Informed consent was obtained in accordance with local ethical guidelines and with the Helsinki Declaration of 1975.

DISCUSSION

Histiocytoses have recently been reclassified in 5 different groups based on a combination of clinical, ra-

Fig. 1. Clinical and histopathological features of the patient. The patient came to our attention with yellowish plaques limited to periorcular and perioral regions (A, C). During the first 2 years of follow-up the lesions slowly increased in volume and extended to columnella (D) and after 5 years they presented as thick tumor/nodular lesions and confluent plaques extending to the forehead, zygoma, eyelids, outer nostrils and mentalabial sulci (B, E). Skin biopsy revealed a dense and polymorphic histiocytic infiltrate (F) made up of large cells with abundant and often foamy cytoplasm (G) and multinucleated giant cells of the Touton (H) and Langhans type, admixed with small lymphocytes and neutrophils.
The presence of BRAF mutations in a significant percentage of patients with histiocytosis and the consequent hyper-activation of the MAPK-pathway seems to play an important role in histiocytic disorders and they have been proposed as diagnostic markers for some entities (e.g. ECD) (13). To the best of our knowledge, the present report is the only one that characterizes XD on a molecular level. Due to the limited amount of literature concerning the molecular landscape of XD, we consider it an important topic to be investigated. Even though the differential benefit of molecular analysis in histiocytoses has recently been denied, molecular characterization is important in order to gather information about the etiology and possibly prognostic stratification in such a rare disorder (13).

The standard therapy strategy for XD is still undefined, although, several therapeutic strategies have been described (14). A review on XD patients, with long-term follow-up, recognized a subset of cases with therapy-unrelated spontaneous partial or complete resolution of lesions (15). Beside these data, several other papers reported progression and/or death of XD patients even after aggressive chemotherapy regimens; consequently, the best therapeutic approach still needs to be weighed against the patient’s clinical severity (4, 11).

In conclusion, we described a very unusual case of XD. Our patient’s features conform to the clinical heterogeneity of histiocytoses and show how differential diagnosis, prognostic stratification and therapeutic approach to NLCH may be incredibly troublesome. Future works should point out the clinical-pathological overlaps between NLCH and perhaps adopt a descriptive nomenclature (as for langerhans cell histiocytosis) allowing for an easier approach to therapeutic decisions.

The authors have no conflicts of interest to declare.

REFERENCES


Comments from the Editorial Office: Please shorten the text by about 200 words to fit this within the 2-page limit of a Short Communication.
### Table S1. Summary of the main clinical-pathological features characterizing non-Langerhans-cell histiocytosis

<table>
<thead>
<tr>
<th></th>
<th>Erdheim-Chester disease</th>
<th>Xanthoma disseminatum</th>
<th>Adult xanthogranuloma</th>
<th>Progressive nodular histiocytosis</th>
<th>Benign cephalic histiocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F</td>
<td>3:1</td>
<td>2.5:1</td>
<td>3:1</td>
<td>2/3:1</td>
<td>2:1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55–60</td>
<td>25–40</td>
<td>20–40</td>
<td>10–30</td>
<td>0–3</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Clinical-pathological, radiological and molecular (?)</td>
<td>Clinical-pathological</td>
<td>Clinical-pathological</td>
<td>Clinical-pathological</td>
<td>Clinical-pathological</td>
</tr>
<tr>
<td>Bone</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>CNS/Diabetes insipidus (DI)</td>
<td>30% DI. Neurodegenerative CNS involvement described.</td>
<td>40% DI. CNS lesions, uncommon.</td>
<td>Uncommon</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Skin</td>
<td>Xanthelasma (33%), papules, plaques.</td>
<td>Xanthelasma, papules (confluent) plaques, nodules.</td>
<td>Single papules or nodules. Less often multiple papules</td>
<td>Hundreds of large nodules or tumor-like lesions all over the skin surface. Mucosal involvement</td>
<td>Several small papules distributed on head and neck region only</td>
</tr>
<tr>
<td>Histology</td>
<td>Polymorphic histiocytic infiltrate with foamy cells (prevalent especially in late phase of disease), Touton giant cells and sometimes (PNH) spindled histiocytes. Background with mixed inflammatory infiltrate.</td>
<td></td>
<td></td>
<td></td>
<td>Monomorphic non-foamy, non-epitheliomorphic histiocytic infiltrate admixed with few lymphocytes.</td>
</tr>
<tr>
<td>Electron microscopy</td>
<td>Lipid vacuoles, myeloid bodies, highly developed endomembrane system, lysosomes, phagosomes.</td>
<td></td>
<td></td>
<td>Coated vesicles, comma-shaped bodies (20%)</td>
<td></td>
</tr>
<tr>
<td>Immunohistochemistry</td>
<td>CD163+, CD68/PGM1+, CD68/KP1+, CD14+, CD4+, FXIIIa+, Vimentin+, S100+/-, CD1a–, CD207–.</td>
<td></td>
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The table highlights the great overlap among these entities, which makes a correct diagnosis difficult to make.