

CLINICAL REPORT

A Case of Generalized Eruptive Histiocytosis

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Histiocytoses are a heterogeneous group of diseases, characterized by the accumulation of reactive or neoplastic histiocytes in various tissues. Generalized eruptive histiocytosis belongs to cutaneous non-Langerhans' cell histiocytoses and is a rare, generalized, self-healing disorder that usually follows a benign clinical course. Herein, we report a case of generalized eruptive histiocytosis in a 41-year-old woman with peculiar clinical and histological features. Clinically, the papules showed a marked distribution into the seborrhoeic areas of the trunk, with a great tendency to coalesce. Furthermore, immunohistochemical labelling demonstrated that the histiocytes were positive for CD68, but negative for CD34, S100, CD1a and XIIIa factor. This is the second report of generalized eruptive histiocytosis with a negative XIIIa factor. We discuss the differential diagnoses of the clinical picture and emphasize that this benign cutaneous disorder should be subjected to close follow-up, owing to the possibility of evolution to a more severe type of histiocytosis or the association with underlying diseases. Spontaneous regression was observed in this actual case. Key words: generalized eruptive histiocytosis; non-X histiocytoses; non-Langerhans histiocytoses; XIIIa factor; atypical.

(Accepted September 28, 2006.)

Acta Derm Venereol 2007; 87: 533–536.

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Generalized eruptive histiocytosis (GEH) is a rare, benign, self-healing and generalized, non-X histiocytosis, initially described by Winkelmann & Müller in 1963 (1). Since its first report, more than 30 cases, including 16 children, have been described. Clinically, it is characterized by recurrent crops of asymptomatic, small, firm, tan to reddish papules, symmetrically distributed over the face, trunk and proximal limbs, which may involute spontaneously, leaving macular pigmentation. Mucous membrane lesions are rare and visceral involvement has not been observed, although there are some reports where an association with rheumatic fever (2), exanthema subitum (3) or an underlying neoplasm was noted (4–7). Histological examination shows a monomorphous

proliferation of benign histiocytes without deposition of lipids, iron or mucine. Electron microscopy reveals that these cells may possess various markers, such as comma-shaped bodies, dense bodies and regularly laminated bodies, but no Birbeck granules. Herein we report a case of GEH in a 41-year-old woman with peculiar clinical and immunohistochemical features.

CASE REPORT

A 41-year-old woman presented with a 3-month history of progressive appearance of brown to reddish and slightly elevated macules and papules, symmetrically distributed on the seborrhoeic areas of the trunk and extensor surface of both upper arms (Figs 1 and 2). The lesions showed a remarkable tendency to coalesce. The face and distal extremities remained unaffected as well as the mucous membranes. The lesions were neither painful nor itchy. Apart from hypercholesterolemia treated with simvastatine (Zocor®), the patient's general health was good. Physical examination did not reveal any abnormalities. Laboratory investigations showed a leukocyte count of 3320/μl (normal, 4000–10000/μl), with no anomalies in the differential blood analysis. Cholesterol levels were slightly elevated (256 mg/dl). Other laboratory investigations revealed normal or negative results (erythrocyte sedimentation, serum chemistries, immunoglobulin levels, angiotensin converting enzyme, C-reactive protein, rheumatoid factor, antinuclear antibodies, thyroid hormones and serological tests for hepatitis B virus, hepatitis C virus, Epstein-Barr virus, human immunodeficiency virus and syphilis). Chest X-ray, abdominal ultrasonography and ophthalmological examination revealed no extracutaneous involvement. Light microscopy showed a thinned and flattened epidermis. Just below this, there was a circumscribed, dense, cellular infiltrate composed of histiocytic cells, which contained large oval nuclei with scanty chromatin and an abundant, light, vesicular and poorly defined cytoplasm (Fig. 3). In addition, there were some lymphocytes and occasional mast cells admixed with the histiocytes. Multinucleate giant cells and foamy cells were absent. Iron and fat deposits were not observed and an Alcian blue staining ruled out interstitial mucine. Immunohistochemical labelling demonstrated that the histiocytes



Fig. 1. Reddish and slightly elevated macules and papules, symmetrically distributed on the trunk, which presented a remarkable tendency to coalesce.



Fig. 2. Erythematous papules on both upper arms.

were positive for CD68, but negative for CD34, S100, CD1a and XIIIa factor (Fig. 4). Electron microscopy studies did not reveal Birbeck granules.

A diagnosis of GEH was established, taking in consideration clinical, histopathological, ultrastructural and immunohistochemical criteria. The patient was closely followed-up during the next months. No treatments were started because of the reported benign nature of this disorder and its tendency to resolve spontaneously. Eleven months after the initial eruption the lesions had disappeared completely.

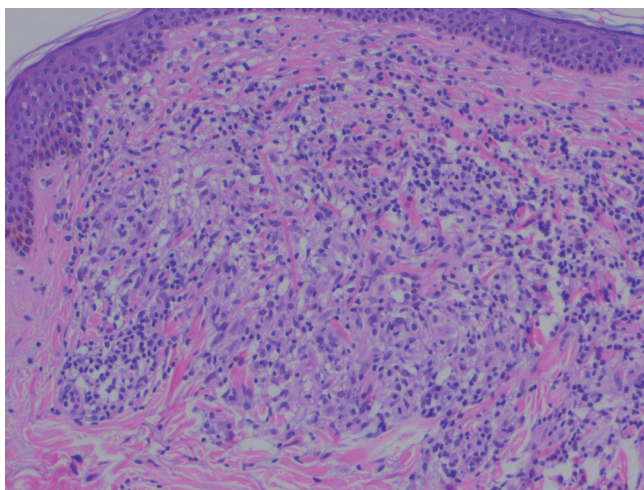


Fig. 3. Thinned and flattened epidermis with a circumscribed and dense cellular infiltrate composed of histiocytic cells localized in the papillary dermis. Multinucleate giant cells and foamy cells were absent (haematoxylin and eosin (H&E) $\times 20$).

DISCUSSION

Our patient showed an asymptomatic papular eruption, histologically composed of a monomorphous histiocytic infiltrate, CD68 positive but CD1a and S-100 negative and without Birbeck granules, which was compatible with a non-X histiocytosis, despite negativity for XIIIa factor. Among non-X histiocytoses, the most likely diagnosis of our patient was GEH, which was established by exclusion of the other non-X histiocytoses. Benign cephalic histiocytosis was ruled out because the age of the patient. Lipidic histiocytosis (papular xanthoma, xanthoma disseminatum and juvenile xanthogranuloma) were excluded in view of the colour of the lesions, the absence of foamy cells and negative fat stain. Multicentric reticulohistiocytosis usually starts in the fourth to sixth decades of life, but the absence of arthropathy and acral lesions, together with lack of giant cells with ground-glass cytoplasm in the biopsy, dismissed this possibility. Progressive nodular histiocytoma was ruled out by the absence of oral and conjunctival lesions and the histopathological pattern. On the other hand, due to the negativity of XIIIa factor, those non-X histiocytoses derived from histiocytes other than the dendrocyte phenotype had to be considered. Progressive mucinous histiocytosis, sinus histiocytosis with lymphadenopathy, diffuse plane xanthomatosis, familial haemophagocytic lymphohistiocytosis, familial sea-blue histiocytosis, necrobiotic xanthogranuloma and virus-associated haemophagocytic syndrome were ruled out because of clinical, histological and immunohistochemical different profiles.

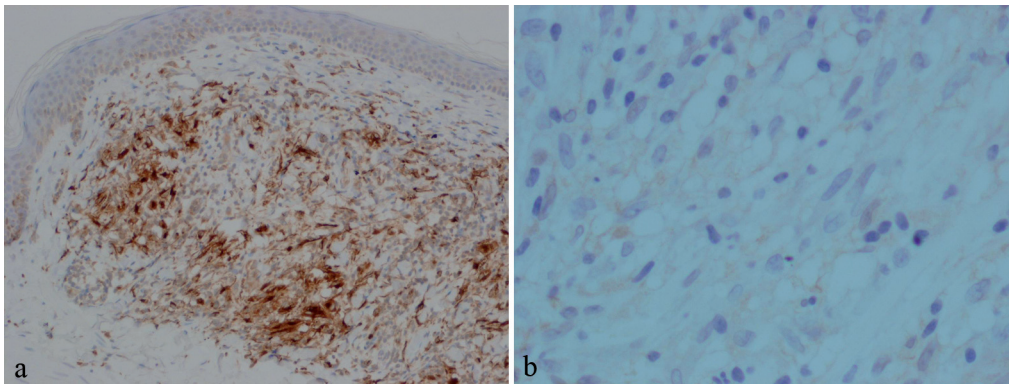


Fig. 4. Immunohistochemical labelling demonstrated that the histiocytes were (a) positive for CD68, $\times 20$, but (b) negative for XIIIa factor, $\times 40$.

Winkelman & Müller described in 1963 (1) the typical diagnostic features of GEH: (i) widespread, essentially symmetric, multiple lesions, particularly involving the trunk and proximal limbs and, rarely, the mucous membranes; (ii) distinct flesh-coloured 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.

Our patient fulfilled these criteria, except for the tendency of the lesions to coalesce. However, when a revision of the literature was made, some examples of GEH where lesions coalesce (6–9) could be found. Two of these patients presented with an underlying haematological neoplasm (6, 7). Our patient was evaluated carefully for this possibility, but all the laboratory investigations were within normal ranges. In addition, the spontaneous resolution does not support an underlying disease.

Other clinical variants have been reported. In children, lesions of GEH are not always symmetrically distributed, but may be localized and become xanthomatous (10, 11). Also, a case with resemblance to molluscum contagiosum has been described (12). These reported cases suggest that clinical characteristics are not as strict as described by Winkelman & Müller (1). In addition, some cases which precede the classical presentation of xanthoma disseminatum (13–15), multiple juvenile or adult xanthogranulomas (14), multicentric reticulohistiocytosis (14) and indeterminate cell histiocytosis (14, 16) or show an overlap to xanthoma disseminatum (8, 16), juvenile xanthogranuloma (17) or indeterminate cell histiocytosis (9) has been reported. These reports support the theory that non-Langerhans' cell histiocytoses may represent a spectrum of diseases, rather than discrete separate entities (18). However, some conditions do not evolve subsequently to other disorders, as in our case and according to the initial Winkelman & Müller description. So, Jang et al. (19) proposed that GEH could be divided into 2 subsets: an indifferent stage of other histiocytic disorders and a specific condition without subsequent disorder. Nevertheless, there

are no clinical, histological or laboratory markers that may predict patient's evolution, so a close follow-up is mandatory.

In conclusion, we report a new case of GEH, a rare non-X histiocytosis, with some clinical and immunohistochemical peculiarities; the papules showed a marked distribution over the seborrhoeic areas of the trunk with a great tendency to coalesce and factor XIIIa was negative by immunohistochemical labelling. In a review of the medical literature, we could find only one case of GEH with negative XIIIa factor (20). Although most of the patients with GEH will suffer a spontaneous involution, close follow-up is necessary to evaluate an association with underlying diseases or evolution into other types of more severe histiocytoses.

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