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Case Report

Can Hansen's disease mimic histiocytosis? Histiocytosis a possibility in nonresponsive and incompletely investigated cases of Hansen's disease

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Abstract Generalized eruptive histiocytosis (GEH) is a rare histiocytosis of the skin that presents in adults as multiple asymptomatic skin colored papules and nodules on the face, trunk and proximal upper limbs in a symmetrical manner. The lesions occur in crops and regress on their own. Clinical and histopathological examination differentiates this condition from other histiocytoses and from the more common disease leprosy, which it mimics closely. We describe a case of GEH mimicking Hansen's disease (HD).

Key words
Generalized eruptive histiocytosis, histiocytosis, Hansen's disease, histoid leprosy, skin colored papules.

Introduction

Generalized eruptive histiocytosis (GEH) is a rare type of non-Langerhans cell histiocytosis (NLCH) that presents usually in adults as multiple asymptomatic, symmetric skin colored papules on the face, trunk and arms with flexural sparing.[1] The disease may mimic several other diseases, Hansen's disease (HD) being one of them in the Indian context. We describe a case of GEH in a female mimicking Histoid HD.

Case report

A 26 year old female presented to us with chief complaints of multiple raised lesions over the face, trunk and arms since 3 months **(Figure 1a,1b,1c)**. The lesions were asymptomatic and first appeared on the face. Newer crops had been appearing on the body, with the earliest ones showing slight reduction in size and tendency for spontaneous regression. There was no history of sensory loss, tingling, numbness, joint pain or weight loss. Similar disease was not present in any family member. The patient revealed that she had been diagnosed as a case of Hansen's disease by some local health care center and had taken treatment for one year but without any improvement. On examination, she was found to have multiple, asymptomatic, skin colored to slightly erythematous nodules and flat papules of the size 5-10 mm diameter on the malar area of the face, forehead, lower trunk, and extensor aspect of the arms. The lesions over the face showed tendency to coalesce. The mucosae, hair, nails, palms and soles were unaffected. Physical examination revealed no nerve thickening or anaesthesia. Systemic examination was unremarkable. Routine investigations (Blood counts, renal and liver function tests, blood sugar) were normal. Slit skin smear was negative for acid fast bacilli (AFB) and venereal

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Figure 1 Multiple, brownish papules and nodules distributed bilaterally over the malar area of the face, and forehead (a), extensor aspect of arm (b) and lower back (c) many of which are showing clinical regression

disease research laboratory (VDRL) test was non-reactive. Chest radiograph and abdominal ultrasonography showed no abnormality. Skin biopsy from the back showed full thickness of dermis filled with nodular aggregations of large histiocytes and a small number of lymphocytes. Fite Faraco stain and Gomori methanamine stains for AFB and fungi were negative. Immunohistochemical analysis showed positivity for CD68 and was negative for CD 1a and S-100. Electron microscopy was not done due to non-availability. Based on these findings, a diagnosis of GEH was made.

Discussion

Histiocytoses are a group of rare diseases characterized by proliferation of histiocytes and was classified for the first time in 1987 into 3 groups: type I (Langerhans cell histiocytosis or LCH), type II (non-Langerhans cell histiocytosis) and type III (malignant histiocytosis).[2] Generalized eruptive histiocytosis (GEH) is a type II histiocytosis. However, the distinction between Langerhans and non-Langerhans cell histiocytosis became questionable with evidence of a fifth of patients of Erdheim Chester disease developing LCH and both diseases showing same gene mutations and same complications like diabetes insipidus and neurodegenerative disease.[3] This led to a revised classification of the disorders of histiocytes by the Histiocyte society. According to this classification, GEH is a histiocytosis of the 'C' group (non-Langerhans cell histiocytosis of the skin) and from the xanthogranuloma family **(Table 1)**.[3]

Winkelmann and Muller in 1963 were the first to describe this disease in three adult patients.[4] GEH presents as erythematous to brownish, asymptomatic, symmetrically distributed papules

Table 1 Revised classification of Histiocyte society (2016).[3]

1.	Histiocytosis of the L group	Langerhans cell histiocytosis (LCH)	
		Indeterminate cell histiocytosis (ICH)	
		Erdheim Chester disease (ECD)	
		Mixed ECH and LCH	
2.	Non Langerhans cell histiocytosis of skin and mucosa: C group	Cutaneous non LCH: Xanthogranuloma family	Juvenile xanthogranuloma (JXG)
			Adult xanthogranuloma (AXG)
			Solitary reticulohistiocytoma (SRH)
			Benign cephalic histiocytosis (BCH)
			Generalized eruptive histiocytosis (GEH)
			Progressive nodular histiocytosis (PNH)
		Cutaneous non LCH: non xanthogranuloma family	Cutaneous Rosai Dorfman disease (RDD)
			Necrobiotic xanthogranuloma (NXG)
			Cutaneous histiocytosis not otherwise specified
		Cutaneous non LCH with a major systemic component: Xanthogranuloma family	Xanthoma disseminatum (XD)
		Cutaneous non LCH with a major systemic component: non xanthogranuloma family	Multicentric reticulohistiocytosis (MRH)
3.	Histiocytosis of the R group	Familial Rosai Dorfman disease (RDD)	Faisalabad syndrome
			FAS deficiency RDD
			Familial RDD not otherwise specified
		Sporadic Rosai Dorfman disease (RDD)	Classical RDD
			Extranodal RDD
			Neoplasia associated RDD
4.	Malignant histiocytosis: M group	Primary	Skin, lymph node , digestive system, central nervous system or disseminated
		Secondary	Secondary to follicular lymphoma, lymphocytic leukemia, hairy cell leukemia, acute lymphoblastic leukemia, other histiocytosis or another hematologic neoplasia
5.	Histiocytosis of the H group	Primary	Monogenic inherited conditions
		Secondary	Associated with infections, malignancies, rheumatological conditions, transplantation, iatrogenic immune activation, iatrogenic immune suppression, other non Mandelian conditions and due to unknown origin

on the face, upper limbs and torso with lesions occurring in crops. There is no extracutaneous involvement.[2] It has been reported to be associated with acute monocytic leukemia and myelodysplastic syndrome.[5,6] Histological evaluation shows dermal infiltration with monomorphic histiocytes. Electron microscopy demonstrates that cells lack Birbeck granules but have concentric laminated bodies.[7] Immunohistochemistry is positive for CD 68 lysozyme, alpha 1 antitrypsin, CD 11b, HAM 56, Mac 387, CD 14b and factor XIIIa.[8] Antigen markers provide an important means to classify the disease. **Table 2** shows a brief review of the usual reaction patterns of various antigen markers in various histiocytosis. Spontaneous remission is seen and is attributed to apoptosis.[9] The disease is generally benign and leaves behind hyperpigmentation.[7] Treatment of persistent disease might be needed and includes corticosteroids, PUVA, hydroxychloroquine and thalidomide.[8,10]

Differential diagnosis in our case included histoid HD, a disease for which she had taken treatment for one year from some local health care center but did not improve. It seems that patient was not sufficiently investigated for HD and was diagnosed it on the clinical basis alone. Histopathology was not carried out. The presence of papules and nodules over the body, involvement of face and forehead near the eyebrows gave the false impression that the patient suffered from HD, which is more common in our part of the world. However, the absence of anaesthesia, nerve thickening,

Table 2 Antigenic markers of hstiocytoses.

Histiocytosis	*CD 1a*	*S-100*	*CD 207 (Langerin)*	*CD 68*	*Factor XIIIa*
Langerhans cell histiocytosis	+	+	+	-	-
Indeterminate cell histiocytosis	+	+	-	+	+/-
Erdheim Chester disease	-	Weakly +	-	+	+
Juvenile xanthogranuloma	-	-	-	+	+
Adult xanthogranuloma	-	-	-	+	+
Solitary reticulohistiocytoma	-	-	-	+	+
Benign cephalic histiocytosis	-	-/+	-	+	+
Generalized eruptive histiocytosis	-	-	-	+	+
Progressive nodular histiocytosis	-	-	-	+	+
Necrobiotic xanthogranuloma	-	-	-	+	-
Xanthoma disseminatum	-	-	-	+	+
Multicentric reticulohistiocytosis	-	-	-	+	+/-
Rosai Dorfman Disease	-	+	-	+	-

negative slit skin smear and absence of AFB on histology suggested otherwise. Progressive nodular histiocytosis (PNH) is another close differential in our case. PNH affects any age group and presents as generalized, discrete, yellow colored papules and nodules predominantly over the face and mucosal involvement.[11] Histology shows xanthomatized histiocytes and mononuclear infiltration in the early stages of the disease and spindle shaped cells in a storiform pattern in the later stages.[12] However, unlike GEH, PNH does not regress and is associated with systemic diseases.[13] The absence of mucous membrane and flexural involvement and no lipids on histopathology rules out xanthoma disseminatum (XD). Multicentric reticulohistiocytosis presents in elderly and shows acral involvement and arthropathy.[14] Benign cephalic histiocytosis is a disease of children while juvemile xanthogranuloma (JXG) and papular xanthoma show foamy cells on histology. Due to similar clinical features and histopathology, some authors are of the view that GEH may represent the initial stage of macrophage diseases like PNH, JXG and XD.[15]Sarcoidosis, secondary syphilis, post kalaazar dermal leishmaniasis and cutaneous T-cell lymphoma can mimic GEH clinically but are easily ruled out based on histopathology and other laboratory investigations.

The presentation of GEH is clinically similar to histoid HD. Sharath *et al.* in 2011 have described a similar case of GEH mimicking leprosy in a 28 year old woman from South India.[16] She was treated at a local health care center for HD but failed to respond. It is important to keep this disease in mind. This will prevent erroneous diagnosis, and avoid unnecessary treatment and social stigmatization of the patient for HD.

Conclusion

Generalized eruptive histiocytosis can simulate histoid HD and cause diagnostic difficulty. This case highlights the need for proper evaluation of all patients of HD for correct diagnosis and management.

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