Yellow papules and nodules in an infant

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An 11-month-old infant presented with asymptomatic, reddish-yellow, monomorphic papules, and nodules on the skin of the face, ears, trunk, and upper extremities, which had slowly increased in number in the past 6 months (Figs 1 and 2). A few lesions had undergone spontaneous regression without scarring. No systemic or mucosal involvement was noted. Mental and physical development was normal. A punch biopsy was taken from a 7-month-old lesion, and staining with CD68 and S100 was performed.

**Question 1: What is the most likely clinical diagnosis?**

- A. Cutaneous mastocytosis
- B. Juvenile xanthogranuloma (JXG)
- C. Generalized eruptive histiocytosis (GEH)
- D. Benign cephalic histiocytosis (BCH)
- E. Langerhans cell histiocytosis (LCH)

**Answers:**

- A. Cutaneous mastocytosis—Incorrect. Mastocytosis is characterized by proliferation of mast cells caused by a mutation of the KIT gene on chromosome 4q12. The maculopapular form is characterized by yellow-orange papules appearing mainly during infancy. The diagnosis is based on the specific histopathologic findings.
- B. JXG—Incorrect. JXG is a benign, self-healing, non-LCH characterized by solitary or multiple yellow-red papules on the skin and, occasionally, in other organs. The histopathologic findings change with the age of the lesion.
- C. GEH—Incorrect. GEH is an exceedingly rare non-LCH presenting with many flesh-colored to red macules and papules that develop in groups, mainly occurring in adults. It may represent the initial stages of a variety of macrophage disorders, such as JXG, xanthoma disseminatum, and progressive nodular histiocytosis, which appear to form parts of a continuous spectrum.
- D. BCH—Correct. BCH is a rare non-LCH. Our patient meets all four of the diagnostic criteria of Gianotti et al: onset of disease within the first 3 years of life; location of skin lesions on the scalp and absence of lesions on the hands, feet, mucous membranes, and internal organs; spontaneous complete remission of symptoms; and monomorphic infiltration of histiocytes that do not express S100 and CD1a (Fig 3).
- E. LCH—Incorrect. The clinical appearance varies: yellow-brown scaly papules, nodules, or plaques combined with fever, lymphadenopathy, osteolytic lesions, and often hepatosplenomegaly. LCH is a diverse disease characterized by a clonal growth of immature Langerhans cells with mutations of BRAF in half of cases.

**Question 2: What are the special stains used to confirm the diagnosis of BCH?**

- A. Giemsa stain
- B. Toluidine blue stain
- C. CD117 marker
- D. CD68 marker
- E. S100 marker

**Answers:**

- A. Giemsa stain—Incorrect. Giemsa stain is a mixture of methylene blue, eosin, and Azure B. It is specific for the phosphate groups of DNA and attaches itself to regions of DNA where there are large amounts of adenine–thymine bonding. It stains human and bacterial cells purple and pink, respectively, and helps to differentiate them. It can be used to specify mast cells.
- B. Toluidine blue stain—Incorrect. Toluidine blue stain is a basic thiazine metachromatic dye with a high affinity for acidic tissue components. It stains nucleic acids blue and polysaccharides purple. Because it stains mastocyte granules purple, it is used for diagnosis of mastocytosis.
- C. CD117 marker—Incorrect. The CD117 protein is a transmembrane tyrosine kinase growth factor receptor that is the product of c-kit gene expression. Marking with CD117 occurs in a variety of tumor types, although strong positivity is present mainly in mast cell disease and gastrointestinal stromal tumors, for which CD117 is the preferred marker.
- D. CD68 marker—Correct. CD68 marker is a marker for macrophages. CD68 is a protein highly expressed by cells in the monocyte lineage, including monocytic phagocytes, osteoclasts, and circulating macrophages, and by tissue macrophages, Kupffer cells, and microglia. It may play a role in macrophage phagocytic activities.
E. S100 marker—Incorrect. S100 marker is a marker for Langerhans cells, as they are characteristically decorated by S100 protein. It is used as a marker for neural crest cells (Schwann cells and melanocytes) and is used to diagnose melanoma.4

Question 3: What histologic features are associated with this diagnosis?

A. Infiltrate, predominantly in the upper third of the dermis, varies from sparse and perivascular to larger aggregates of mast cells and scattered eosinophils.

B. Dense, poorly demarcated infiltrate of small histiocytes involving the dermis and sometimes the upper subcutis as well. The cells are polygonal or spindle-shaped and have indistinct cytoplasmic borders. Foamy histiocytes and various numbers of Touton cells are also seen.

C. Infiltrate of histiocyte-like cells, often spindle-shaped, in the upper and mid dermis.

D. Diffuse infiltrate of histiocytes, mainly in the upper dermis. The cells have oval or reniform vesicular nuclei and ill-defined pale cytoplasm.—Correct—BCH. The typical histologic finding is diffuse infiltrate of histiocytes, mainly in the upper dermis (Fig 3) or could be lichenoid-like right under the epidermis. The cells have oval or reniform vesicular nuclei and ill-defined pale cytoplasm. Grouped lymphocytes and occasional eosinophils can be seen. Xanthomatization can be seen in lesions of long duration. The histiocytes in BCH express typical non-Langerhans markers, including CD68 (Fig 4), factor XIIIa, and CD16, but S100 is negative.3

E. Clusters and sheets of larger ovoid cells with abundant eosinophilic cytoplasm and nuclei that are indented reniform-like immediately beneath the epidermis and have little tendency to extend to the reticular dermis.—Incorrect—LCH. Histologic examination shows clusters and sheets of large cells in the papillary dermis that sometimes invade the epidermis. The cells are ovoid with abundant eosinophilic cytoplasm, uniform, with an eccentric, indented or reniform, sometimes “coffee-bean”-shaped nucleus. Langerin (CD207), CD1a, and S100 are positive.3

Abbreviations used:

BCH: benign cephalic histiocytosis
GEH: generalized eruptive histiocytosis
JXG: juvenile xanthogranuloma
LCH: Langerhans cell histiocytosis

Conflicts of interest

None disclosed.

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