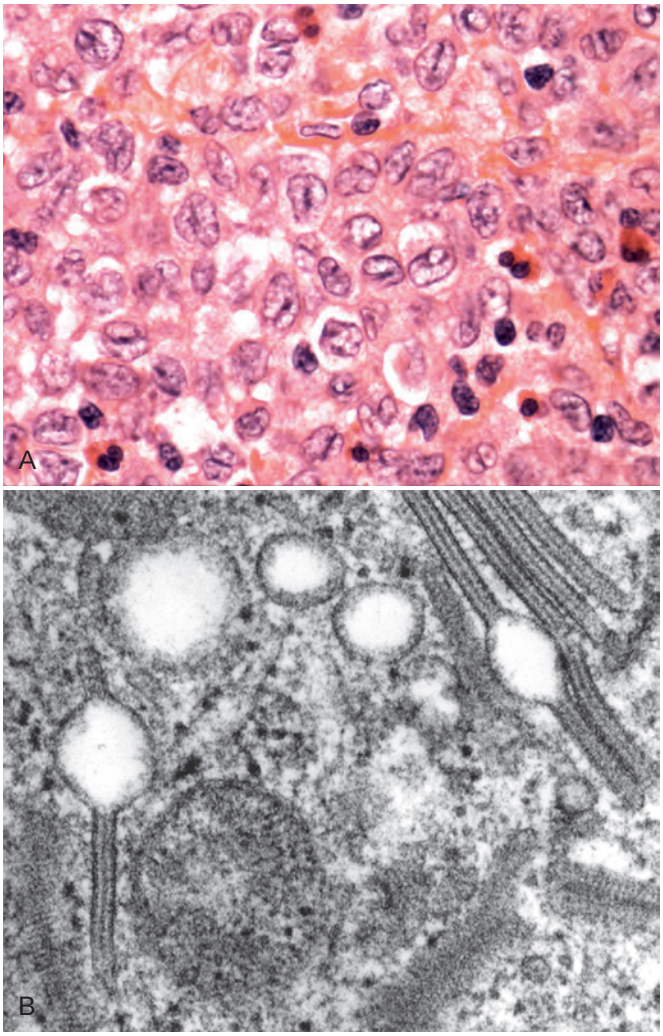

Figure 13-38 Langerhans cell histiocytosis. **A,** Langerhans cells with folded or grooved nuclei and moderately abundant pale cytoplasm are mixed with a few eosinophils. **B,** An electron micrograph shows rodlike Birbeck granules with characteristic periodicity and dilated terminal end. (**B,** Courtesy Dr. George Murphy, Department of Pathology, Brigham and Women's Hospital, Boston, Mass.)

Regardless of the clinical picture, the proliferating Langerhans cells have abundant, often vacuolated cytoplasm and vesicular nuclei containing linear grooves or folds (Fig. 13-38*A*). The presence of *Birbeck granules* in the cytoplasm is characteristic. Birbeck granules are pentalaminar tubules, often with a dilated terminal end producing a tennis racket-like appearance (Fig. 13-38*B*), which contain the protein langerin. In addition, the tumor cells also typically express HLA-DR, S-100, and CD1a.

Langerhans cell histiocytosis presents as several clinicopathologic entities:

- *Multifocal multisystem Langerhans cell histiocytosis (Letterer-Siwe disease)* occurs most frequently before 2 years of age but occasionally affects adults. A dominant clinical feature is the development of cutaneous lesions resembling a seborrheic eruption, which is caused by infiltrates of Langerhans cells over the front and back of the trunk and on the scalp. Most of those affected have concurrent hepatosplenomegaly, lymphadenopathy, pulmonary lesions, and (eventually) destructive osteolytic bone lesions. Extensive infiltration of the marrow often leads to anemia, thrombocytopenia, and a predisposition to recurrent infections, such as otitis media and mastoiditis. In some instances the tumor cells are quite anaplastic; such tumors are sometimes referred to as Langerhans cell sarcoma. The course of untreated disease is rapidly fatal. With intensive chemotherapy, 50% of patients survive 5 years.
- *Unifocal and multifocal unisystem Langerhans cell histiocytosis (eosinophilic granuloma)* is characterized by proliferations of Langerhans cells admixed with variable numbers of eosinophils, lymphocytes, plasma cells, and neutrophils. Eosinophils are usually, but not always, a prominent component of the infiltrate. It typically arises within the medullary cavities of bones, most commonly the calvarium, ribs, and femur. Less commonly, unisystem lesions of identical histology arise in the skin, lungs, or stomach. *Unifocal lesions* most commonly affect the skeletal system in older children or adults. Bone lesions can be asymptomatic or cause pain, tenderness, and, in some instances, pathologic fractures. Unifocal disease is indolent and may heal spontaneously or be cured by local excision or irradiation. *Multifocal unisystem disease* usually affects young children, who present with multiple erosive bony masses that sometimes expand into adjacent soft tissue. Involvement of the posterior pituitary stalk of the hypothalamus leads to diabetes insipidus in about 50% of patients. The combination of calvarial bone defects, diabetes insipidus, and exophthalmos is referred to as the *Hand-Schüller-Christian* triad. Many patients experience spontaneous regression; others can be treated successfully with chemotherapy.
- *Pulmonary Langerhans cell histiocytosis* represents a special category of disease, most often seen in adult smokers, which may regress spontaneously upon cessation of smoking. These lesions have been described as reactive proliferations of Langerhans cells, but fully 40% are associated with BRAF mutations, suggesting that in many instances, they too are neoplastic in origin.

One factor that contributes to the homing of neoplastic Langerhans cells is the aberrant expression of chemokine receptors. For example, while normal epidermal Langerhans cells express CCR6, their neoplastic counterparts express both CCR6 and CCR7. This allows the neoplastic cells to migrate into tissues that express the relevant chemokines—CCL20 (a ligand for CCR6) in skin and bone, and CCL19 and 21 (ligands for CCR7) in lymphoid organs.