Langerhans cell histiocytosis: A complex recurrent disease

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A six-year-old boy was referred to a paediatric hematologist/oncologist with recurrent, painful skull masses. Skeletal survey and computed tomography revealed lytic lesions in his calvarium (Figure 1) and a silent lesion in his right humerus. Positron emission tomography-computed tomography scan confirmed involvement of these sites. A biopsy of the skull mass showed infiltrates of pathogenic Langerhans cells, staining positive for CD1a, Langerin and S100, and containing Birbeck granules on electron microscopy. Of note, 14 months earlier, the boy had a soft tissue mass removed by surgical curettage from the lateral wall of his left orbit but no adjuvant therapy. The pathology of both lesions was consistent with Langerhans cell histiocytosis (LCH).

The boy's treatment at this time included vinblastine and prednisone for a year, with regression of all lesions. Three years later, another skull mass appeared and surgical curettage again showed pathogenic Langerhans cells. Meanwhile, he had developed excessive thirst and polyuria. A water deprivation test confirmed diabetes insipidus. A brain magnetic resonance imaging scan showed enhancement and thickening of his infundibular pituitary stalk, suggestive of LCH involvement. In view of this new development, a paediatric endocrinologist became involved in managing the diabetes insipidus and is closely observing any further pituitary complications. Because LCH has the potential to recur despite successful therapies, sometimes with significant sequelae, close supervision by a multidisciplinary care team is essential (1).

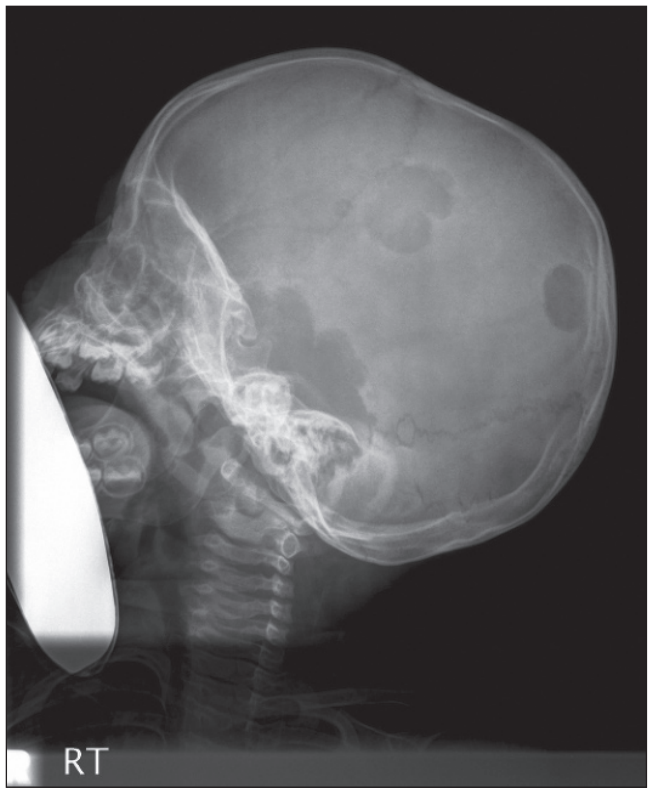

Figure 1) *Lytic skull lesions. Reproduced with permission from Dr Bruce Crooks*

LEARNING POINTS

- LCH is a rare disease of unknown causes, characterized by the proliferation of pathogenic Langerhans cells and cytokine overproduction, and causes inflammation, infiltration and destruction of many tissues in the body.
- Due to the recognition of the pathogenic Langerhans cell as a common cause, LCH now includes previously described conditions ranging from the acute fulminant disseminated Letterer-Siwe disease, through the intermediate Hand-Schüller-Christian disease and histiocytosis X, to the more chronic and often solitary eosinophilic granuloma.
- Although the Langerhans cells are not generally believed to be cancerous, the clinical manifestations of organ infiltration and the potential for fatal disease, along with a clonal population, argue in favour of a malignant process.
- Presentations of LCH include the following:
  - skin rashes (resembling seborrheic dermatitis [Figure 2] in infants) resistant to usual therapies;

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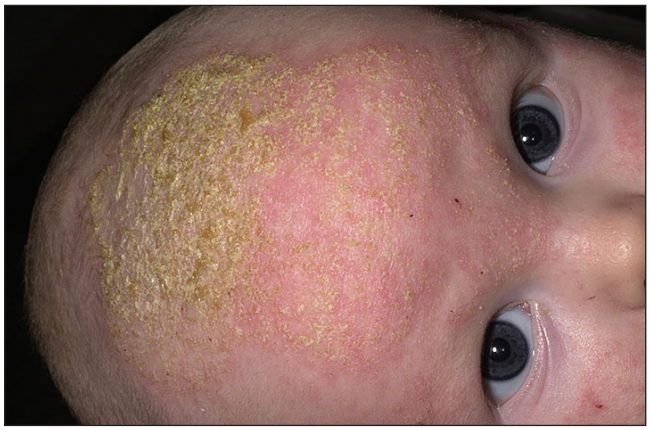

Figure 2) *Seborrheic dermatitis. Reproduced from <www.dermnet.com/seborrheic-dermatitis>*

  - unifocal or multifocal bony lumps, frequently affecting skull and facial bones;
  - central nervous system disease, often involving the pituitary/infundibulum and causing diabetes insipidus; or
  - fulminant multiorgan disease of infancy, which may be fatal.
- The most common treatments range from observation alone, surgical curettage with or without intralesional steroids, nonsteroidal anti-inflammatory agents (eg, indomethacin) or cytotoxic agents (eg, vinblastine, prednisone or cladribine). Fulminant multiorgan disease or recurrent/resistant disease may be treated with biological modifiers (eg, cytokine inhibitors) or may require hemopoietic stem cell transplantation.
- Due to its rarity and diverse presentations, the true incidence and burden of LCH are poorly understood, with estimates ranging from 2.24 to 8.9 per million children. Most data are European and are limited by being taken from institutional series or regional/national registries only. LCH can also occur in adults, although even less is known regarding incidence and outcome in this group.
- The recent British Paediatric Surveillance Unit (2) and French national studies (3) were more comprehensive, seeking cases from multiple sources, and reported incidences of 4.12 per million children (aged zero to 14 years) and 4.6 per million children, respectively. The British study identified 17% of cases from outside the British Paediatric Surveillance Unit program, implying that many cases are not seen by paediatricians.
- In North America, delays to diagnosis may be due to low awareness and understanding of LCH, and patients can first present to different specialties such as paediatrics, orthopedics, neurosurgery, ophthalmology, ear, nose and throat, and dermatology. Most cases in children are eventually managed by paediatric hematology/oncology specialties.
- The current national study of LCH aims to collect national data over two years, primarily via the Canadian Paediatric Surveillance Program but also by parallel survey of other allied specialty physicians and surgeons to collect additional cases and to help identify pathways of referral. Results are important for the development of a national registry to optimize care and research for LCH patients.

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The Canadian Paediatric Surveillance Program (CPSP) is a joint project of the Canadian Paediatric Society and the Public Health Agency of Canada, which undertakes the surveillance of rare diseases and conditions in children and youth. For more information, visit our Web site at <www.cps.ca/cpsp>.