INTRODUCTION
Langerhans Cell Histiocytosis (LCH) is a rare and broad-spectrum disease caused by uncontrolled proliferation of pathologic Langerhans cell resulting in localized and systemic organ infiltration. The clinical presentation can be unspecific and varies between individuals depending on the anatomical location and organ involvement. In view of bony infiltration is the most common in LCH, clinicians have to deal with the challenge of diagnosis dilemmas such as Giant Cell Tumour, Ewing’s sarcoma, osteogenic sarcoma, plasmacytoma, osteomyelitis or bony metastasis, particularly from neuroblastoma. Hence, it requires an excellent multidisciplinary team to establish the diagnosis and start targeted treatment early to prevent fatal complications. The treatment modalities include surgery, immunosuppressive therapy, chemotherapy or in combination. Recently, a seven months old boy presented to our centre with one-week duration of left cheek swelling and left eye proptosis. After detailed clinical evaluation together with imaging and biopsy, the lesion over the bilateral sphenoid and left zygoma were concluded to be Langerhans Cell Histiocytosis (LCH).

CASE REPORT
A 7 months old baby boy presented with sudden onset of left cheek swelling for five days which were rapidly increasing in size. The swelling was painless, with no discharge, not associated with fever, no shortness of breath, and no other swelling elsewhere, and the baby was still able to tolerate feeding well. Antenatal history was uneventful and he was born via spontaneous vaginal delivery with a birth weight of 3.77 kg. The baby’s vaccination was up to date according to the Malaysian National Immunization program, with no history of hospitalization or surgery.
no known allergy history, or no family history of malignancy. Clinical examination revealed a firm mass measuring 4.0 x 3.0 cm at the left zygomatic region and lateral orbital wall with mild proptosis of the left eyeball (Figure 1).

Figure 1. White arrow showing the mass measuring 4.0 x 3.0 cm occupied over the left zygomatic region and left lateral orbital wall. It was firm in consistency, fixed to the underlying structure, non-tender, no erythematous skin and no overlying skin changes.

Otoscopy, intraoral, anterior rhinoscopy and neck examinations are normal. He was admitted to paediatric ward for further investigation. Contrast-enhanced computed tomography (CECT) of the brain revealed heterogenous enhancing soft tissue masses noted along the bilateral sphenoid wing. There was associated bony erosion of the bilateral greater wing of the sphenoid and frontal process of the left zygoma bone (Figure 2). The mass extended into the orbital cavity causing compression onto the lateral rectus muscle, eye globes and lacrimal glands bilaterally (Figure 3).

Figure 2. Axial view of CECT brain revealed two heterogenous enhancing soft tissue masses along bilateral greater wing of sphenoid measuring approximately 2.5 cm (AP) x 2.5 cm (W) x 2.9 cm (CC) on the right and 2.3 cm (AP) x 3.0 cm (W) x 2.8 cm (CC) on the left. (AP= anteroposterior; W= width; CC = craniocaudal diameter). There was an evidence of bony erosion over the right greater wing of sphenoid (red arrow) and left greater wing of sphenoid (yellow arrow).
Figure 3. Coronal view of CECT brain revealed two heterogenous enhancing soft tissue masses extending into the orbital cavity causing compression onto the lateral rectus muscle, lacrimal gland and eye globe bilaterally (red arrow).

He underwent incisional biopsy of left zygomatic mass under general anaesthesia and the histopathology examination showed abundant of Langerhans cell infiltration (Figure 4). Immunohistochemistry shows the Langerhans cells are positive to S100, CD1a, and CD68 which concluded the diagnosis of Langerhans Cell Histiocytosis (Figure 5).
Bone marrow aspiration and trephine biopsy revealed no evidence of Langerhans cell infiltration. Ultrasound abdomen, chest X-ray and skeletal survey were arranged prior to treatment showed no spleen, liver, lung and other bony involvement. He was referred to a paediatric oncologist and family conference was done regarding the treatment plan. Taking into consideration of single system LCH with cranium involvement in this patient, he was commenced on LCH III treatment protocol which include oral prednisolone 40mg/m² daily in 3 divided doses for 4 weeks duration then taper over 2 weeks together with chemotherapy (intravenous Vinblastine 6 mg/m² = 1.8 mg weekly x 6 doses). After six weeks of treatment initiation, the repeated CECT brain showed the heterogenous enhancing lesions over the bilateral sphenoid wings were significantly reduced in size with the measurement difference of 0.4 cm (AP) x 1.6 cm (W) x 1.7 cm (CC) on the right side and 0.4 cm (AP) x 1.6 cm (W) x 1.0 cm (CC) on the left side. (Figure 6).

Figure 5. Immunohistochemistry staining show positive to S100 (5a; white arrow), CD 68 (5b; grey arrow), and CD1a (5c; black arrow) finalized the diagnosis of Langerhans cell histiocytosis.

Figure 6. Repeated axial view of CECT brain 6 weeks after initiation of treatment revealed heterogenous enhancing lesion along the sphenoid wing were significantly reduced in size, with approximate measurement of 2.1 cm (AP) x 0.9 cm (W) x 1.2 cm (CC) on the right and 1.9 cm (AP) x 1.4 cm (W) x 1.8 cm (CC) on the left. Bony erosion over the right (red arrow) and left greater wing of sphenoid (yellow arrow) remained the same.
Hence, continuation of LCH III treatment protocol was commenced with pulse of oral prednisolone 40mg/m² daily in 3 divided doses, day one to five every 3 weeks as well as intravenous Vinblastine 6mg/m² =1.8mg every 3 weeks started from week 7 till end of month 6 since therapy started. As of today, patient is in his week 21 of therapy and are tolerating well to current treatment regime without any unforeseen complications. His parents were very committed to the treatment schedule and grateful for the good response of their child’s illness. He was planned for repeat CT brain and skeletal survey after completed 6 months of current treatment regime.

Discussion
Historically, the term Langerhans Cell Histiocytosis (LCH) has many names, which include Letterer-Siwe disease, eosinophilic granuloma, and Hand-Christian-Schuller disease until in the year 1953, it was collectively grouped as histiocytosis X by Lichtenstein before it was standardized by Writing Group of Histiocyte Society in the year 1987 as LCH [10]. LCH is a rare occurrence and behaves aggressively, but it lacks the histopathological evidence of malignancy [11,12]. The histologic hallmark for definite diagnosis of LCH is based on the evidence of proliferation of multinucleated Langerhans’ cells, presence of histiocytes with sheets of eosinophils and Birbeck’s granules on electron microscopy examination or immunohistochemistry staining showed positivity for CD1a, S100, and Langerin (CD207) [11,13,14]. This is in keeping with the patient’s histopathology findings reported here.

Although LCH can occur in every part of the body, bony involvement is the most common, with reported cases of 80%, followed by the skin (33%), pituitary gland (25%), liver 15%, spleen 15%, lymph nodes (5-10%), and central nervous system (CNS) (2-4%) [15,16]. Among the bony infiltration, the skull vault is the most commonly affected (40%), followed by the vertebra (18%), lower extremities (17%), pelvis (10%), and upper extremities (8%) [16]. From the reported cases base on anatomical region, head and neck involvement are common, ranging from 73 to 90% [11,13,17]. Most importantly, LCH lesions of the temporal, orbital, sphenoid, ethmoidal, maxilla, zygomatic bone, paranasal sinuses, as well as anterior or middle cranial fossa, are associated with an overall 25% higher risk for CNS involvement and threefold greater risk for diabetes insipidus [16,18,19].

In view of the involvement of sphenoid and zygoma bone in this case, the clinicians must have a high index of suspicion to look for central diabetes insipidus development during surveillance follow-up as it is the most common neuroendocrine manifestation secondary to posterior pituitary involvement with an incidence of 8-12% [20]. The second most common CNS findings that should be highlighted are the CNS neurodegeneration recognized by irreversible cerebellar syndrome or learning difficulties and bilateral symmetric lesions at the dentate nucleus on neuroimaging [21]. Hence, the development milestones of this boy should be assessed and charted till school age.

LCH can present as either isolated unifocal or multifocal single-system (SS-LCH; 75% of patients) or multisystem disease (MS-LCH; 25% of patients) involving two or more organs [17]. According to the Histiocyte Society, it can be subdivided into four subtypes: SS-LCH without lung or risk organ involvement, SS-LCH with lung involvement, MS-LCH without risk organ involvement, and MS-LCH with risk organ involvement [15]. The “risk organ” involvement referring to the liver, spleen, lung, and haematopoietic system are associated with poorer prognosis and higher mortality [15]. Moreover, Gadner et al. found out that children under two years old are associated with risk organ involvement, not responsive to initial treatment and hence increase the mortality rate by 1.6-fold for each additional organ involved [22]. Furthermore, Yagci et al. pointed out that elevated acute phase reactants in the blood, such as C-reactive protein, erythrocyte sedimentation rate, and lactate dehydrogenase, are associated with poorer overall survival [6]. Fortunately, our patient reported here has no risk of organ involvement from the imaging, and the laboratory parameters are within the normal range.

Although the aetiology of LCH is still unknown, some authors suggest this as a reactive disease in response to infection with contribution from the oncogenesis and dysregulation of the immune system [8,23,24]. This can be attributed from the heightened inflammatory response elicited by neoplastic cells. The inflammatory cells are known to secrete proteolytic enzymes, cytokines and chemokines which act as mitogenic for the neoplastic cells and indirectly potentiate tumour proliferation and growth. Besides, Egeler et al. speculated the pathogenesis of LCH may be due to genetic defects,
abnormal response to infection, autoimmune disease, or a combination of these factors [23]. According to Geissmann et al., LCH cells are functionally immature dendritic cells in the chronic form of the disease [25]. Drugs that induce their maturation may enhance cell killing by Cytotoxic T lymphocytes. A more recent study suggests that LCH is a neoplastic process of myeloid origin characterized by activation of the MAPK/ERK signalling pathway, with significant inflammatory component [19].

According to the Histiocyte Society, the treatment modalities for LCH are based on the number and type of organs involved and whether organ dysfunction is present [26]. Patients with the unifocal single-system disease usually require local treatment or observation [19]. This strategy holds true for the isolated skeletal disease as most of the bony lesion will regress spontaneously [27,28]. In the event of persistent disease, simple curettage or regression is generally sufficient for lesion less than 5 cm whereas systemic therapy is reserved for those lesions more than 5 cm, lesions at risk of progression to the CNS or lesions at critical area where local therapy is not feasible. Radical excision for lesion more than 5 cm should be avoided due to risk of permanent disfigurement, bony deformities, extensive bony defect and prolonging healing time [15,27,28]. The role of intralesional steroid injection is controversial with some authors claimed to aid in healing after local therapy while others do not recommend due to its increase risk of recurrence [27-29].

However, for a patient with craniofacial bone lesion with intracranial extension, a standard six months regime of prednisolone and Vinblastine are recommended based on the LCH III treatment protocol by the Histiocyte Society [19]. These drugs are relatively non-toxic and well tolerated in combination when compared with cytotoxic drugs such as etoposide [11,15]. This is in resemblance with the oncologist management in our patient reported here even though the long-term outcome is still unknown. From the previous reported case study, the clinical response to the initial six weeks of treatment is a good marker of further disease progression which will determine the length and the intensity of the treatment in poor or good responders [11,15]. Increased treatment duration for at least one year reduces the risk of disease reactivations in multisystem disease based on the LCH III protocol and DAL-HX 83/90 studies [11,15,19,30]. Patients with risk organ involvement who do not respond after 12 weeks of treatment should switch to salvage therapy which include combination of 2-chlorodeoxyadenosine and cytarabine as well as stem cell transplantation [30]. With regards to radiotherapy, it is no longer recommended in paediatric age group due to the risk of developing secondary malignancy and solid tumours, particularly sarcoma and brain tumours in the irradiation field [8,15]. Nevertheless, stereotactic radiosurgery (SRS) targeted for the neurological LCH has been reported either as a first-line treatment or at some point in their treatment course demonstrating tumour regression and stability of tumour [27]. Recommended follow-up should be at least five years after the end of treatment or five years after the last disease recurrence without receiving systemic treatment or until adolescence [15].

**Conclusion**
Early establishment of LCH diagnosis and commencement of treatment with the cooperation of multidisciplinary teams are essential to prevent disease progression and fatal complications. The mainstay of treatment for single system LCH involving craniofacial bone include immunosuppressant, chemotherapy or in combination. Long term surveillance follow-up is utmost important not just for the disease recurrence per se, but also to monitor for the potential sequela of intracranial involvement such as diabetes insipidus, neurological deficit and development milestone delay.

**Abbreviations**
LCH: Langerhans Cell Histiocytosis  
CECT: Contrast-enhanced computed tomography  
CNS: Central nervous system  
SS: Single system  
MS: Multisystem

**References**


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