Case Report

Langerhans' Cell Histiocytosis (LCH) in Adolescence Presented with Central Diabetes Insipidus: A Case Report

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A 19-year-old Thai man presented with symptoms of central diabetes insipidus, exopthalmos and multiple ostolytic lesions of the cranial vault. Skin biopsy showed strongly positive CD 1a and S100. Electron microscopy showed rod shape and pentalaminar granules called "Birbeck" granules, a diagnosis compatible with Langerhans' cell histiocytosis (LCHs) or histiocytosis X. He was successfully treated with systemic chemotherapy.

***Keywords**: Langerhans' cell histiocytosis (LCHs), Histiocytosis X, Diabetes insipidus, Birbeck*

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Langerhans' cell (LC) is an important antigen-presenting cell of the immune system. LCs differ from other histiocytes in being CD1a-positive[1]. The classic electron microscopic finding of pentalaminar Birbeck granules has reached a new level of understanding[2]. These structures have been identified as infoldings of the cell membrane, possibly because of antigen processing. The granule protein has been isolated, and a gene for what is now known as " Langerin" has been cloned[3]. Langerhans' cell histiocytosis (LCHs) or histiocytosis X is an idiopathic disorder characterized by a proliferation of histiocytes. It is generally considered to include a spectrum of disorders such as eosinophilic granuloma (EG), Hand-Schuller-Christian (HSC) disease and Letterer-Siwe (LS) disease which vary in prognostic results[4,5]. LCH is a rare disease with an incidence of approximately 1 case per 2 million children. Males are more frequently affected than females; age at presentation varies from a few months to 15 years[6]. The aim of this report is to present a case of LCH in spectrum of Hand-Schuller-Christian (HSC) disease in an adolescent patient suffering from central diabetes insipidus, bilateral exopthalmos and skull osteolytic in geographic pattern for 10 years before definite diagnosis of Birbeck granules by electron microscopy (EM).

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Case Report

A 19-year-old Thai male had a history of polydipsia and polyuria of about 10 litres per day for 10 years. The patient had previously been seen by several physicians and diagnosed as having diabetes insipidus. His medication regime before admission was: indomethacin 25 mg twice daily, moduretic 0.5 tablet once daily. After admission to our endocrine clinic, he underwent a water deprivation test for diabetes insipidus. The laboratory results at the beginning of the test were serum osmolarity 313 mOsm/l, urine osmolarity 89 mOsm/l; after taking desmopressin (Minirin) 0.1 ml nasally, his serum osmolarity was 320 mOsm/l and urine osmolarity was 484 mOsm/l. On physical examination, his vital signs were normal, but he had mild tenderness at both parietal areas. Both of his eyeballs were markedly protruding (exopthalmoses), his chest wall appeared normal, there was mild minimal protrusion of the medial head of the right clavicle near

the right sternoclavicular joint, no abnormal breathing sound, there was no hepatosplenomegaly.

Laboratory result showed; Complete blood count: Hemoglobin 10.8 gm/dL, hematocrit 30.8%, white blood cell count 8,300/μL, neutrophil 59.0%, eosinophil 5.0%, monocyte 5.0%, lymphocyte 31.0%, platelet 547,000/mm^3. Urine analysis: specific gravity 1.015, pH6, serum electrolyte: sodium 146 mEq/L, potassium 4.2 mEq/L, chloride 110 mEq/L, bicarbonate 30 mEq/L, calcium 8.8 mEq/L, BUN/creatinine 6.0/0.8 mg/dL, liver function test: total bilirubin 0.24 mg/dL, direct bilirubin 0.08 mg/dL, alkaline phosphatase 145 U/L, SGOT 18U/L, SGPT 9U/L, albumin 3.8 g/dL, globulin 4 g/dL, alpha-fetoprotein 1.54 ng/ml, β-HCG 2 mlU/ml and ESR 100 mm/hr.

Other endocrinological tests: morning cortisol level 17.20 μg/dl (6.2-19.4), follicular stimulating hormone (FSH) level 3.1 ng/dl (1.5-12.4), luteinizing hormone (LH) 7.7 ng/dl (1.3-13.0), testosterone 11.2 ng/ml (10.0-35.0).

Skull x-rays showed multiple ostolytic lesions of the cranial vault vary 1-4 cm in size. The borders were well-defined; some were punched out lesions and had beveled edges. The lesions were geographic osteolytic and involved all cranial fossa (Fig. 1). The cervical spine showed partial collapse of C7. Chest x-ray showed no pulmonary infiltration, normal heart and hili. The thoracic cage showed osteolytic lesions at the proximal and distal parts of the right clavicle and osteolytic lesions of the inferior portion of the scapula. The lesions were sclerotic rims. Thoracic and lumbar spine AP, lateral view showed partial collapse of the T5, T7, T9 of the vertebral bodies causing some degree of scoliosis. Long bone surveys showed well-defined osteolytic lesions with sclerotic rims of about 1 cm noted at the metaphysis of proximal parts of both humeri and 3 cm lesions at the metaphysis of the distal part of the right femur and an ill-defined lesion at the right proximal femur. Pelvis radiography showed multiple osteolytic lesions with sclerotic rim at the bilateral iliac wings, bilateral inferior rami of pubis 1-2 cm in size. Mandible panoramic view showed osteolytic lesions involving the whole body of the mandible causing floating teeth.

Magnetic resonance image: absence of posterior pituitary gland bright spot indicating an impaired pathway in the hypothalamus and multiple scattering lesions with diploic space (Fig. 2). Bone scans

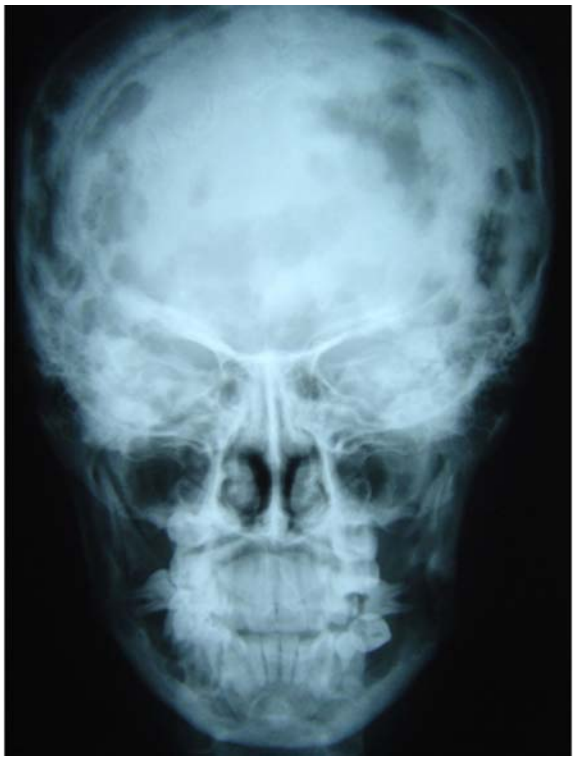

Fig. 1 Skull x-ray showed multiple ostolytic lesions of the cranial vault call "geographic osteolytic"

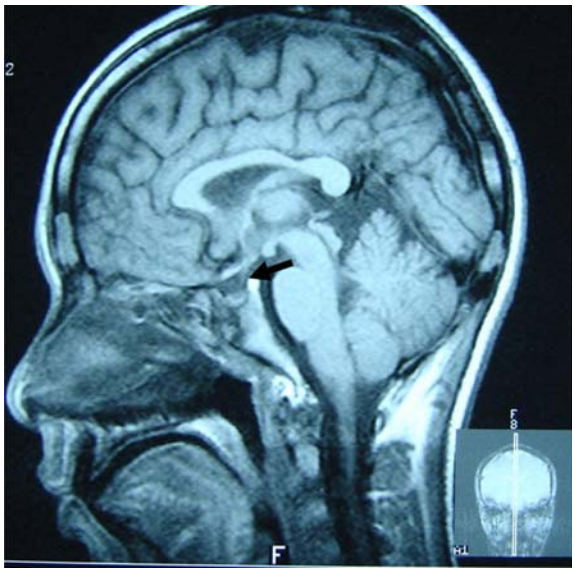

Fig. 2 Absence of posterior pituitary gland bright spot (arrow) indicating an impaired pathway in the hypothalamus and multiple scattering lesions with diploic space on magnetic resonance image (MRI)

showed multiple radiotracer defect uptake in the skull and increased uptake at the medial end of the right clavicle, left 5th, 9th and 10th rib, proximal and distal femur. High resolution computer tomography (HRCT) of the lung showed a 1 cm lung cyst at the superior segment of the right lower lobe, two precarinal adenopathy.

Bone biopsy showed normal bone architecture. A skin immunohistochemistry biopsy was done at the parietal area of the skull, which had erythematous macules which demonstrated positive for CD3 in most affected cells and positive for PGM-1 in some cells, but CD20-negative. CD1a and S-100 protein demonstrated strongly positive (Fig. 3 and Fig. 4). Electron microscopy findings demonstrated rod shape and trilayer granules called Birbeck granules (Fig. 5).

The patient was diagnosed with Langerhans' cell histiocytosis by clinical pathology. This patient commenced treatment with prednisone (PDN): 1 mg/kg/day (60 mg), as a 4 week course, tapering over a period of 2 weeks with vinblastine (VBL) 6 mg/m^2 intravenous bolus (10 mg), on day 1, 8, 15, 22, 29, 36 and continuation treatment starting at day 43 after initial treatment: 6-mercaptopurine (6-MP): 30 mg/m^2 (50 mg) daily until completion of treatment, prednisone (PDN): 1 mg/kg/day (60 mg) day 1-5 every 3 weeks until completion of treatment, vinblastine(VBL): 6 mg/m^2 intravenous bolus (10 mg) day 1 every 3 weeks until completion of treatment (starting 3 weeks after the last VBL injection of the initial treatment or intensification). The total duration of the treatment was six months.

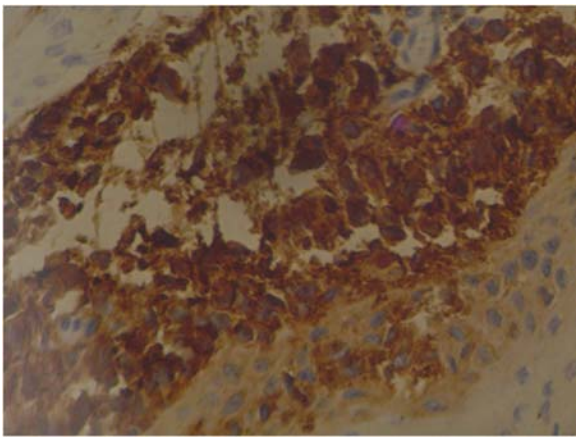

Fig. 3 CD1a protein demonstrated strongly positive (CD1a x 400)

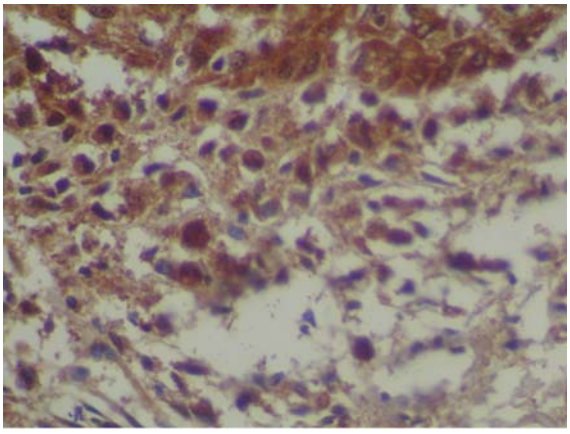

Fig. 4 Diffuse S-100 positive Langerhans' cells illustrated (S-100 x 400).

Fig. 5 Electron microscopy demonstrated rod shape and Trilayer granules called "Birbeck granules"

Discussion

This patient is classic Hand-Schuller-Christian disease, as originally described. Clinical features may also include defects in the mandible, long bones, pelvis, ribs and spine. Classically, this syndrome describes a triad of osteolytic defects, diabetes insipidus and exophthalmos, which occurs in only 10 percent of chronic differentiated cases. The lungs and pleura are affected in 30 percent of patients.

The Histiocyte Society has established criteria necessary for the presumptive, designated, and definitive diagnosis of Langerhans' cell histiocytosis (LCH) based on immunohistochemistry and histopathology[7,8]. Biopsy of suspicious lesions and staining for CD1a and S100 protein or anti-langerin is needed in order to confirm the diagnosis. Electron microscopy to identify Birbeck granules is performed

less frequently because of time and expense. In our case the initial bone biopsy was unable to make a diagnosis, which made it difficult to decide on definitive treatment. A skin biopsy was taken from the skin lesions present as coalescing, scaling or crusted, brown to flesh-colored papules and the pathology report indicated only mild chronic perifolliculitis; however, electron microscopy later identified Birbeck granules.

Surgery, radiation therapy and chemotherapy are treatment options for LCH. These modalities can be used either alone or in combination, depending upon the extent and severity of the disease[9,10]. Chemotherapy is generally employed for patients with multisystemic LCH, in combination with local steroid injection. Overall, the prognosis is good, with survival rates greater than 90.0% in patients having limited organ involvement. However survival rate are reduced in the presence of multisystem organ involvement and persistently active disease.

A number of presentations indicate that the patient is at high risk of recurrence, complications, or multisystem disease. These include: skeletally mature patients, involvement of more than one bone and involvement of central nervous system (CNS)-risk bones; multisystem involvement requires systemic therapy. In our case we performed chemotherapy for 6 months and reviewed the patient after 1, 2, 3 and 6 months. He improved clinically; he can now work and he has a better quality of life. At present he is managing on a reduced dose of demopressin (0.05 ml nasally once daily) to control polyuria.

Conclusion

This case that shown how difficult to diagnosis of difficult case for appropriate management. An ongoing area of research in the development of innovative treatments for LCH includes immunophenotypic analysis of Langerhans cell activity. Langerhans cells within bone have been identified as immature and poorly immunogenic. Thus, it has been proposed that the development of drugs which enhance maturation of Langerhans cells may be beneficial in the treatment of LCH. Nowaday, there is no universally accepted protocol for the treatment of LCH.

Potential conflicts of interest

None.

References

1. Favara BE. Langerhans' cell histiocytosis pathobiology and pathogenesis. Semin Oncol 1991; 18: 3-7.
2. Seiji M, Shimao K, Fitzpatrick TB, Birbeck MS. The site of biosynthesis of mammalian tyrosinase. J Invest Dermatol 1961; 37: 359-68.
3. Valladeau J, Ravel O, Dezutter-Dambuyant C, Moore K, Kleijmeer M, Liu Y, et al. Langerin, a novel C-type lectin specific to Langerhans cells, is an endocytic receptor that induces the formation of Birbeck granules. Immunity 2000; 12: 71-81.
4. Jones RO, Pillsbury HC. Histiocytosis X of the head and neck. Laryngoscope 1984; 94: 1031-5.
5. Kamoshima Y, Sawamura Y, Sugiyama T, Yamaguchi S, Iwasaki Y, Kubota K. Langerhans cell histiocytosis of the temporal bones with infiltration of temporal muscle: a case report. No Shinkei Geka 2008; 36: 435-9.
6. A multicentre retrospective survey of Langerhans' cell histiocytosis: 348 cases observed between 1983 and 1993. The French Langerhans' Cell Histiocytosis Study Group. Arch Dis Child 1996; 75: 17-24.
7. Schmitz L, Favara BE. Nosology and pathology of Langerhans cell histiocytosis. Hematol Oncol Clin North Am 1998; 12: 221-46.
8. Terracciano L, Kocher T, Cathomas G, Bubendorf L, Lehmann FS. Langerhans cell histiocytosis of the stomach with atypical morphological features. Pathol Int 1999; 49: 553-6.
9. Appling D, Jenkins HA, Patton GA. Eosinophilic granuloma in the temporal bone and skull. Otolaryngol Head Neck Surg 1983; 91: 358-65.
10. Levy R, Sarfaty SM, Schindel J. Eosinophilic granuloma of the temporal bone. Two cases with bilateral involvement. Arch Otolaryngol 1980; 106: 167-71.

รายงานผู้ป่วย แลงเกอร์ฮานเซลล์ ฮิสติโอซัยโตซิส ในวัยรุ่นชายแสดงด้วยอาการเบาจืดจากระบบประสาท ส่วนกลาง

สถิตย์ นิรมิตรมหาปัญญา, ชัยชาญ ดีโรจนวงศ์, ธวัชชัย สุวรรณบรรณ, อรศิริ เสรีรัตน์,อุษากร อุตรภิชาติ, ฐิติ กวักเพทูรย์

ผู้ป่วยชายไทยอายุ 19 ปี มีอาการเบาจืดจากระบบประสาทส่วนกลาง, ตาโปน และภาพทางรังสีของกะโหลกศีรษะ พบลักษณะการแหว่งของกะโหลก การวินิจฉัยแลงเกอร์ฮาน เซลล์ ฮิสติโอซัยโตซิส จากการตัดชิ้นเนื้อบริเวณหนังศีรษะ ส่งตรวจ ย้อมพิเศษด้วย CD1a และ S100 รวมถึงพบ "Birbeck granule" จากการตรวจโดยกล้องจุลทรรศน์อิเล็กตรอน ซึ่งมีส่วนสำคัญมากในการช่วยวินิจฉัยโรค ซึ่งผู้ป่วยได้รับการรักษาด้วยเคมีบำบัด