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Original Article

Langerhans cell histiocytosis and neuroblastoma: report of two cases with follow-up for over 3 years

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Abstract: Langerhans cell histiocytosis (LCH) is a clinically heterogeneous disorder characterized by proliferation of abnormal bone marrow derived dendritic cells. Neuroblastoma (NB) is embryonal tumors that form around sympathetic nerve ganglions. It is the most extracranial malignant tumor type. We present 2 patients who developed LCH and NB. Up to July 31, 2015, these 2 patients have been followed up over 3 years, the prognosis are optimistic. Here we introduce our experiences during the therapeutic process of the 2 cases.

Keywords: Langerhans cell histiocytosis, neuroblastoma, follow up

Introduction

Neuroblastoma (NB) is the most common extra-cranial malignant tumor of childhood. It accounts for 7% of all childhood malignancies, while NB accounts for 10% of childhood cancer mortality. During the maintenance therapy, many children with NB will reappear. But we have followed up the two cases who suffered NB and LCH, both of them accepted the standard therapy. After 3 years, both of the patients have no evidence for recurrence.

Case report

Case 1

A 5.5-months-old girl was admitted in June 2011, because of the skin rash with acute onset and chronic progression. The rash was mainly distributed in the head, cervical, trunk, perineum, which was erythematous papules and a litter higher than the surface of skin. Palpation of the rash is not smooth and the girl had pectus excavatum. She had no fever and bone pain, her weight had no obvious lost. She was diagnosed as eczema and has no response to the therapy.

Histopathology examination of the skin showed that massive amounts of Langerhans cells in the skin tissue under light microscope. Immunohistochemically, the tumor cells were positive for CD1a and CD68, negative for SYN, CgA, CD44, NSE. We can find focal distribution langerhans cells in the superficial layer of dermis under electric mirror. CT scan showed the pulmonary parenchyma and interstitial lesion. Temporal CT showed shadow of soft tissue in both external auditory canals, tympanum and the left mastoid sinuses. Other sites of involvement included lung, skin and ears. Bone marrow aspirate, MRI of the skull and the whole body bone scan were normal.

The patient then enrolled in international association of tissue cells LCH-I. We defined the patient as the high risk group with multi-organ damaged. While, during the evaluation of the system organ, the abdominal ultrasound and the CT revealed a 3.5×3.7×3.2 cm^3 tumor mass behind the peritoneum and a metastasis mass located on the right adrenal. Enhanced CT revealed an occupying lesion in the left side of spine and wrap around the vessels.

We suspect the patient maybe suffered the NB. So, laboratory tests were performed for the

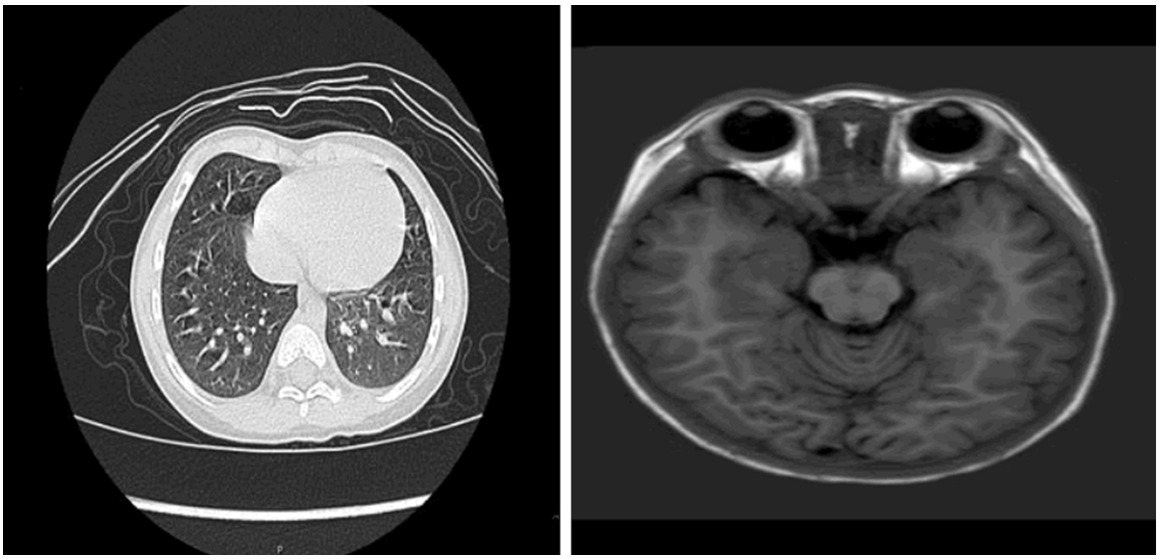

Figure 1. The chest CT scan and cranial MRI were all normal after following up 3.5 years of case 1.

child. The serum neuron-specific enolase (NSE) was 63.8 ng/ml (normal level ≤25 ng/ml). The urine VMA was 2.3 mg/24 hours (normal level ≤13.6 mg/24 hours). To confirm the property of the mass, we carried out the biopsy by laparotomy, acquired the lymph node tissue from the skin, right adrenal and the left enlarged lymph node, CD1a (+), the left lymph node was LCH and CD1a (+), right adrenal NB with poorly differentiated. The tumor cells were positive for NSE, Syn, CgA, CD44, and ALK (partially positive). Fluorescence in situ hybridization (FISH) of tumor cells revealed that N-myc gene was amplified (50 copies). The test of chromosome was normal.

In conclusion, this patient was eventually diagnosed as LCH and NB. The patient received NB protocol chemotherapy and the tumor resection. Meanwhile, she also received the vinblastine combined with prednisone to cure the LCH for 1 year. After the initial 2 courses of etoposide and carboplatin, the patient received the scheduled 2 courses of cyclophosphamide, adriamycin and vincristine. She completed 4 courses of chemotherapy prior to surgery and finished the MRI and CT to assess the response. As the result was well, she then received a surgical excision.

The patient eventually received 7 courses of intensive chemotherapy and then, entered the maintenance therapy period. The rash fades away soon after receiving the chemotherapy. The major drug of maintenance therapy period was vinblastine, prednisone and methotrexate (MTX)/6-mercaptopurine (6-MP) for 1 year. Now, the patient received regular reexamination and evaluation in our hospital, the cranial MRI, chest CT scan (**Figure 1**) and the tumor markers (NSE, LDH, SF) were all normal. Now, we haven't found any evidence for the recurrence.

Case 2

A 22-months-old female was admitted in July 2012, presented with the left frontal mass for one and a half month. She received curettage of the mass in the local hospital. Pathological biopsy revealed a mass of Langerhans cells among the tissue under the light microscope. CD1a, CD68, S-100 (partially), Langerin is positive. The patient was diagnosed as LCH and without any chemotherapy. Half a month later, the abdominal CT revealed a mass of soft tissue shadow.

The patient was suspected as NB and turn to our hospital. The consultation note of pathology department of our hospital showed that CD1a, CD68, S-100 and Langerin are positive. CgA, SYN and NSE are negative. The examination performed after admitting into the hospital to evaluate the patient's condition. The NSE level was 33 ng/ml. The VMA was 2.37 mg/24 hours.

The patient had normal hearing, and skull x-ray revealed destruction evidence in the frontal

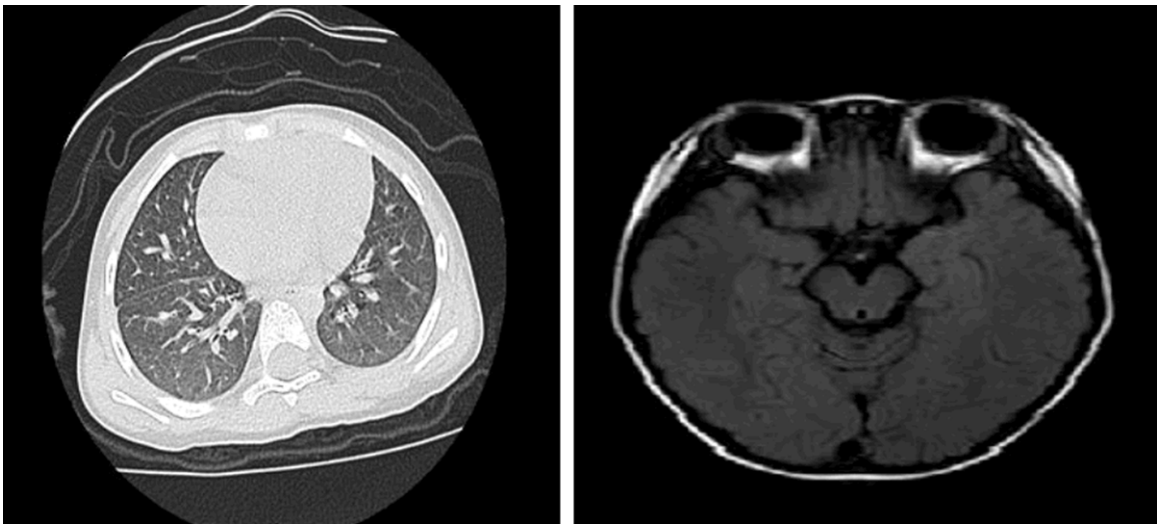

Figure 2. The chest CT scan and cranial MRI were normal after following up 2 more years of case 2.

bone, the abnormality demonstrated as LCH. There was no evidence of destruction in axial skeletons and the appendicular skeletons. The CT scan of lung was normal. The MRI of hypophysis and the bone marrow lesion showed no evidence of LCH. The abdominal enlarged CT scan revealed an ovoid mass at the right front side of the lumbar vertebra in the right middle abdomen. The density among the mass was distinct. Several stippled or stripped calcification can be found. The volume was 5.3×2.8×2.4 cm^3. Enhanced CT the mass imaged obviously. The postcava became flat and be partially covered on the L3 level. The patient received tumorectomy. Pathologic diagnosis as the right retroperitoneal NB with poorly differentiated. NSE, SYN, CgA, CD44, ALK (partially) were positive, CD1a, S-100 and Langerin were negative. FISH of tumor cells revealed that N-myc gene was 3 copies, the chromosome test was normal. PET/CT after the surgery revealed no evidence of micro residual disease.

So, the patient eventually enrolled the LCH-III group and the medium risk group of NB. The patient received 3 courses of etoposide and carboplatin and 2 courses of cyclophosphamide, doxorubicin and vincristine. After the tumor resection, the patient received 3 courses of intensive chemotherapy repeatedly. Meanwhile, the drug of maintenance therapy period was vinblastine and prednisone for 6 months. Now we have followed up the patient for 3 years, the cranial MRI, chest CT scan (**Figure 2**) and the tumor markers (NSE, LDH, SF) were all normal.

Discussion

LCH is a clinically heterogeneous disorder characterized by proliferation of abnormal bone marrow-derived dendritic cells. The disorder ranges from the presence of a solitary bone lesion (eosinophilic granuloma) to disseminated disease associated with multi-organ dysfunction [1]. While the most common presentation of LCH in childhood is a single skull-based mass lesion, bone lesions, can present throughout the skeletal system and are not always associated with a soft tissue mass. Histologically, bone lesions consist of Langerhans cells and other immune cells capable of abundant cytokine release, and typically demonstrate clonality. The treatment of LCH is based on the severity of disease. The pathogenesis of LCH and its relationship to other malignancies is poorly understood.

We present 2 cases of children who developed LCH and NB, while receiving a protocol therapy for LCH and NB. The pathogenesis of LCH is poorly understood. The development of this disease is thought to be related to alterations in immune function, including excessive cytokine release [2, 3]. There have been prior reports of LCH associated with malignancy in both the pediatric and adult populations, either preceding, concurrent with, or following treatment for another malignancy. Depending on the timing of the LCH relative to the diagnosis of the other malignancy, LCH has been thought to be either a reactive process triggered by another cancer or a secondary effect of treatment. This report

emphasizes the necessity to thoroughly evaluate in patients who has diagnosed LCH, although suffer from both diseases at the same time is rare. During the period of therapy, we should reconcile both diseases, chemotherapy for the NB is the major part of our therapeutic schedule.

The NB patient with N-myc gene amplified usually have poor prognosis [4]. But in the first case, we have followed up for over 4 years, she has no evidence to recurrent. During the period of maintenance treatment, we add 6-MP and MTX to cure the disease [5]. So, we hypothesis that 6-MP may be influence the cytokine release, immune system or the micro environment of tumor. Now, the 2 patients have a long term following up.

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Disclosure of conflict of interest

None.

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