World Journal of Hematology

Online Submissions: http://www.wjgnet.com/esps/
wjhematol@wjgnet.com
doi:10.5315/wjh.v2.i3.89

World J Hematol 2013 August 6; 2(3): 89-98
ISSN 2218-6204 (online)

CASE REPORT

Management of adult Langerhans cell histiocytosis based on the characteristic clinical features

Shinsaku Imashuku, Chihiro Shimazaki, Arinobu Tojo, Toshihiko Imamura, Akira Morimoto

Shinsaku Imashuku, Division of Hematology, Takasago-seibu Hospital, Takasago 676-0812, Japan
Shinsaku Imashuku, the NPO for Japan Langerhans Cell Histiocytosis Study Group, Kyoto 602-8566, Japan
Chihiro Shimazaki, Division of Hematology, Social Insurance Kyoto Hospital, Kyoto 603-8151, Japan
Arinobu Tojo, Division of Stem Cell Therapy, Center for Stem Cell Biology and Regenerative Medicine, the Institute of Medical Science, the University of Tokyo, Tokyo 108-8639, Japan
Toshihiko Imamura, Department of Pediatrics, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto 602-8566, Japan
Akira Morimoto, Department of Pediatrics, Jichi Medical University School of Medicine, Shimotsuke 329-0498, Japan
Author contributions: All authors engaged in part in consulting and providing treatment for the patients presented; Imashuku S and Tojo A designed; Imashuku S wrote the paper; Shimazaki C, Imamura T and Morimoto A provided constructive insights in preparation of the paper; all authors approved the final version of the manuscript.
Correspondence to: Shinsaku Imashuku, MD, Consultant, Division of Hematology, Takasago-seibu Hospital, 1-10-41 Nakasuji, Takasago 676-0812,
Japan. shinim95@mbox.kyoto-inet.or.jp
Telephone: +81-79-4470100 Fax: +81-79-4470180
Received: April 11, 2013 Revised: May 10, 2013
Accepted: June 5, 2013
Published online: August 6, 2013

Abstract

To find out the most appropriate management, clinical features of 18 cases of adult multisystem langerhans cell histiocytosis (LCH) have been analyzed. The patients comprising of 9 males and 9 females were median age of 36 years, ranging from 18-53 years at diagnosis. Regarding the initial symptoms, 7 patients (2 males and 5 females) showed central diabetes insipidus (CDI) and other endocrine symptoms with thickened pituitary stalk or a mass at the hypothalamic region. Additional 2 patients initiated the disease with CDI with no immediate diagnosis. In the remaining patients, the disease begun with single (n = 3) or multiple (n = 1) spinal bone lesion(s) in 4 patients (all males), with multiple bone lesions in 3 patients (1 male and 2 females), with single skull lesion in one female patient and with ambiguous symptoms including hypothyroidism in the remaining one male patient. We also recognized the correlation between pregnancy/childbirth and LCH in 4 patients. In terms of treatment, 9 patients received systemic immuno-chemotherapy alone, of which the majority received vinblastine-based chemotherapy while 4 received 2-chlorodeoxyadenosine. Five had a combination of immuno-chemotherapy with surgical resection or radiotherapy, 2 had immunotherapy alone, 2 had surgical resection followed by observation alone to date. Three patients received hematopoietic stem cell transplantation after extensive chemotherapy. In terms of outcome, 15 patients are alive (9 with active disease, 6 without active disease), with a median of 66 mo (range 17-166 mo), two died of disease while the remaining 1 lost to follow-up. Based on these results, we think that early diagnosis and rapid introduction of appropriate treatment are essential, in order to overcome the problems relevant to adult LCH.

Key words: Langerhans cell histiocytosis; Adult; Immuno-chemotherapy; 2-chlorodeoxyadenosine; Childbirth

Core tip: Clinical features and treatment in a total of 18 adult patients with langerhans cell histiocytosis (LCH) were reviewed. We found two major groups regarding the initial symptoms; one was central diabetes insipidus and other endocrine symptoms (n = 9) and the other bone diseases (n = 8; 1 skull, 4 spinal and 3 multiple). We also recognized the correlation between pregnancy/childbirth and LCH in 4 patients. Based on the clinical features and outcomes, early diagnosis and rapid introduction of appropriate treatment are essential, in order to overcome the problems relevant to adult LCH.

Imashuku S, Shimazaki C, Tojo A, Imamura T, Morimoto A. Management of adult Langerhans cell histiocytosis based on the characteristic clinical features. *World J Hematol* 2013; 2(3): 89-98 Available from: URL: http://www.wjgnet.com/2218-6204/full/v2/i3/89.htm DOI: http://dx.doi.org/10.5315/wjh.v2.i3.89

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare lymphoproliferative and granulomatous disease comprising of CD1a-positive LCH cells, T-cell lymphocytes, macrophages, eosinophils and other cells[1-3]. About two-thirds of LCH cases are seen in childhood, with the remaining occurring in adulthood[4]. Information on clinical features in adult LCH patients is limited[5,6]. While pediatric LCH has been extensively investigated, adult LCH remains poorly scrutinized, except for characteristic pulmonary diseases, which is closely related to smoking[7,8]. Epidemiology of non-pulmonary adult LCH is still poorly understood. LCH is an enigmatic disease that is thought to be caused by a pathological combination of oncogenesis and immune dysregulation[1-3]. Aricò *et al*[5] analyzed 274 biopsy-proven adult LCH cases from 13 countries; the mean ages at the onset and diagnosis of disease were 33 years and 35 years, respectively, with single-system LCH (SS-LCH) 31.4% and multisystem disease LCH (MS-LCH) 68.6%. Central diabetes insipidus (CDI) was found in about one third (29.6%) of the patients. The probability of survival in these cases at 5 years post-diagnosis was 92.3%, indicating that the adult LCH is not necessarily a fatal disease, but the highly problematic in adults is the impaired quality of life associated with active disease, particularly of MS-LCH. Based on our previous literature review on 43 Japanese adult cases[4], age distribution showed a peak at 20-40 years of age (31/43 cases, 72%), particularly in females in the 3rd decade. Five cases (11.6%) were older than 55 years. In terms of involved organs, beside lungs (n = 15) which are the most frequently involved organ, bone (n = 11), CDI (n = 10), skin (n = 8), followed by various organs were noted in these adult cases. The LCH in adults excluding isolated pulmonary disease could be comparable with those in childhood; however, the characteristics in adult disease remain elusive. Here, we present a case series on recently treated 18 adult MS-LCH and review clinical features with specific issues relevant to adult patients, including imaging of characteristic findings. Regarding the treatment/outcome, there seems to be a significant progress in recent cases described here, compared to the cases in our previous literature review[4]. In this case series, we also attempted to find out the appropriate therapeutic measures in adult LCH patients.

CASE REPORT

Patients and methods

Adult (> 18 years) LCH cases referred to the authors for treatment and/or consultation during the period of 1999-2012 have been analyzed for clinical characteristics and treatment. Cases of isolated pulmonary LCH were excluded in the analysis. The patients comprising of 9 males and 9 females were median age of 36 years, ranging from 18-53 years at diagnosis. The diagnosis of LCH was confirmed immunohistochemistry [S100 (+), CD1a (+) or CD207 (+)] on the biopsied or resected tumors in all patients. In terms of treatment, besides surgery/radiotherapy or immuno-chemotherapy, all patients with CDI were given nasal desmopressin acetate hydrate (DDAVP) and those with other endocrine symptoms received hormonal replacement therapy. Outcome at the last follow-up was defined as alive with no active disease (ASAD), alive with disease (AWAD), or died. The follow-up period of the 15 patients excluding 1 lost-to follow up and 2 deceased was a median 66 mo (range 17-166 mo). Of these cases, Cases 13-16 were previously published focused on the endocrine problems[9]. Case 17 were included in an analysis of LCH-related neurodegenerative disease[10] and Cases 4 and 17 were also included in a therapeutic trial of LCH[11]. Case 10 was briefly reported as a case of multiple bone lesions[12].

Case 1

A 27-year-old female complained of amenorrhea and polyuria/polydipsia after her second childbirth. She was found to have a mass at the hypothalamic pituitary region (HPR), the biopsy of which revealed LCH. She was treated with radiotherapy (20 Gy) to the CNS mass, oral prednisolone (PSL) and DDAVP. No other LCH lesions developed in this case, thus no other systemic chemotherapy was given. In terms of outcome, she has been lost to follow-up.

Case 2

A 25-year-old female developed amenorrhea and polyuria/polydipsia after her second childbirth. She had a mass at the HPR, and granulomatous lesions at the nasal alar parts as well as thyroid mass, which biopsy revealed LCH. At first she was treated with hydrocortisone, DDAVP and levothyroxine sodium. Four years later, multiple LCH lesions were noted at her scalp, perineal-anal regions, subcutaneous abscess-like lesions at the lumbar area, cervical subcutaneous mass. She was treated with systemic chemotherapy (cyclophosphamide/etoposide/PSL), but remained in a partial remission. Particularly, her recalcitrant fistula-forming subcutaneous lesions were probably related to her poorly controlled diabetes mellitus. Eventually, she died of sepsis-induced disseminated intravascular coagulation (DIC).

Case 3

A 35-year-old female developed multiple masses after childbirth at the right subauricular and subscaplar regions and right 5th rib, which biopsy revealed LCH. She then developed multiple bone lesions at the spine (C2, C4, C5, Th3-4), clivus, occipital bone, as well as subcutaneous

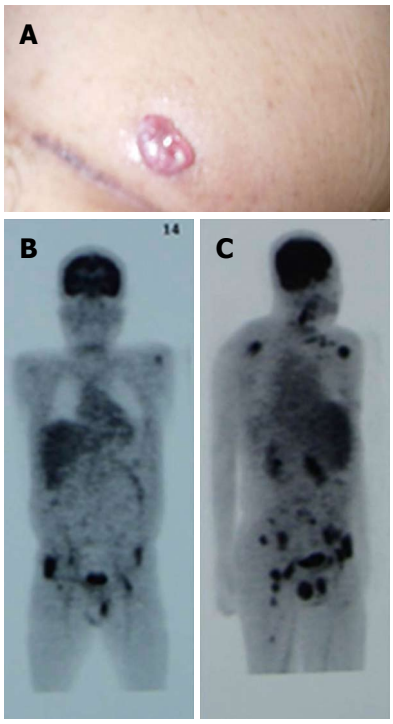

Figure 1 Langerhans cell histiocytosis skin lesions and systemic positron emission tomography imaging. A: Soft papular skin lesion is found at the inguinal area. Biopsy of the lesion revealed the histology of langerhans cell histiocytosis; B, C: Positron emission tomography scan shows multiple lesions, at the scapulas, plevic bones, cervical and inguinal lymph nodes: frontal view (B), lateral view (C).

masses (at her left upper arm and elbow). The lesions at the Th3-4 caused paresis due to spinal compression, which needed laminectomy. She was initially treated with bisphosphonate alone, but thereafter with intensive systemic chemotherapy (JLSG-96 protocol)[13], including vincristine and cytosine arabinoside. However, 2 years later, she needed allogeneic hematopoietic stem cell transplantation (HSCT) because of progressive disease. The patient has currently been alive without active disease (ASAD).

Case 4

A 37-year-old male was found to have CDI, in association with hyper-prolactinemia (seum PRL 56.1 ng/mL). A thickened pituitary stalk was demonstrated on brain magnetic resonance imaging (MRI), which biopsy revealed LCH. Since then he developed multiple bone lesions at spines (cervical, lumbar), bilateral ilium, left sacroiliac joint, and bilateral ribs as well as skin lesions (Figure 1A) and cervical lymphadenopathy. He was treated first with PSL and bisphosphonate followed by systemic chemotherapy (JLSG-96 protocol)[13]. One year later, because of progression of the disease (Figure 1B and C), he received HSCT and has currently been in a state of ASAD.

Case 5

A 40-year-old male complained first of mandibular pain. He was found to have multiple bone lesions (left mandible, left temporal, occipital, bilateral femurs, cervical spines and right petrous bone. Biopsy of the temporal bone lesions revealed LCH. He was treated with irradiation (6 Gy) to the left petrous bone and systemic chemotherapy, including vinblastine (VBL) and PSL followed by the JLSG-96 protocol[13] and bisphosphonate; however, reactivation occurred to C1, C2, right mandible, Th5, bilateral femur distal end. Thereafter, he responded well to the chemotherapy with 2-deoxychloroadenosine (2CDA; cladribine). The patient has currently been in a state of ASAD.

Case 6

A 46-year-old female, who was first noted to have thyroid cysts at age 43, complained of back pain and found to have a compression fracture of Th4. A year later she complained of right rib pain. Positron emission tomography (PET) scan revealed hot spots (SUVmax; 7.0) at the both thyroid lobe (Figure 2A) as well as other numerous hot spots at the deep cervical lymph nodes, right scapula, right ilium as well as right rib. Another year later, right lobe of the thyroid was removed, which was diagnosed as LCH. She also received a resection of right rib, which was also found to be LCH. Since then, she was treated with VBL and PSL; however, treatment was stopped because of VBL neurotoxicity. Thereafter, new bone lesions at the frontal bone, rib, ankle, knee, *etc*. She gave births two children; however, the initiation of LCH was not relevant to her childbirth. The patient has continued to have active disease (alive with active disease, AWAD).

Case 7

A 40-year-old male complained of nuchal and left-shoulder pain without any triggering events. With MRI, he was found to have a mass at the left upper and lower articular processes and part of the left articular arch of C3, which was positive for Ga^{67} bone scintigraphy. This mass was totally resected. Nearly 2 years later, he had a tender and soft swelling at the right sided parietal bone (Figure 2B), which was also positive for Ga^{67} scintigraphy. This tumor was again resected. Both tumors were diagnosed as LCH. Currently at age 46, the patient has been followed up without receiving any systemic chemotherapy and in a state of ASAD.

Case 8

A 40-year-old male was found to have a mass at the left articular arch to the spinous process of C6, which was significantly hot (SUVmax; 6.6) with PET scan (Figure 3). The mass was biopsied, which was diagnosed to be LCH. The CT scan showed the lymphadenopathy at the bilateral axillary as well as inguinal area. Thus, an inguinal node was biopsied, which also showed LCH with complex karyotypes. Past history showed he had a severe atopic dermatitis since age of 20, treated with Protopic (tacrolimus hydrate) ointment. He was treated with systemic chemotherapy [VBL/methotrexate (MTX)/PSL/bisphosphonate]. The patient has currently been treated for active C6 lesion.

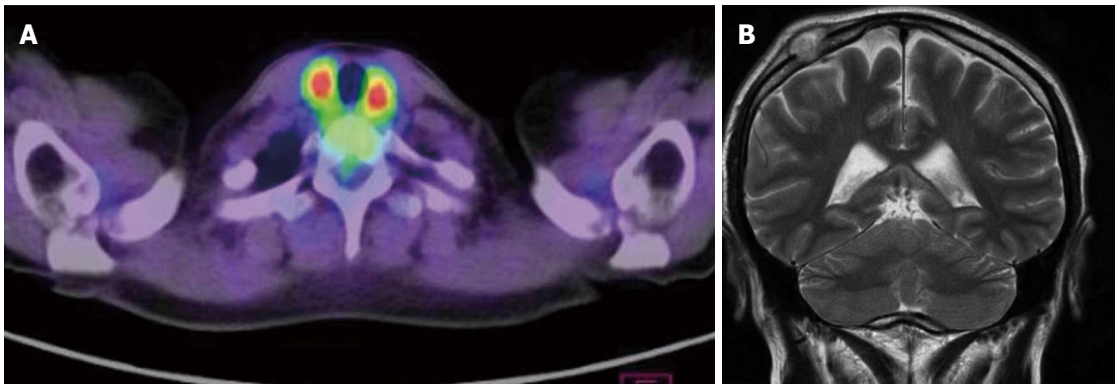

Figure 2 langerhans cell histiocytosis thyroid (A) and skull (B) lesions. A: Positron emission tomography scan shows hot spots (SUVmax = 7.0) at both lobes of thyroid; B: Magnetic resonance imaging (T2W2) shows a mass at the right parietal region.

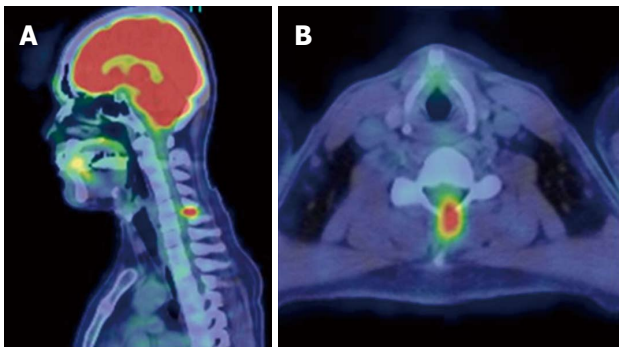

Figure 3 langerhans cell histiocytosis bone lesion at cervical vertebra 6. Positron emission tomography scan shows a hot spot (SUVmax = 6.6) at the spinous process of C6. A: Sagittal view; B: Axial view.

Case 9

A 27-year-old female, who had been treated for atopic dermatitis since childhood, was noted to have a swelling at the right orbit. MRI showed a mass lesion at the right temporal bone extended to the adjacent muscle, which consisted of heterogeneous components (Figure 4A and B). The mass was extensively removed by surgery and the diagnosis of LCH was made. PET scan did not reveal any other suspected lesions. Thus, she was put on observation alone. The patient has been followed up longer than two years without reactivation of the disease. No CDI has occurred and the patient has been in a state of ASAD.

Case 10

A 31-year-old male was first noted to have 1st thoracic spine lesion at age 25, which was biopsied and diagnosed as LCH. Two years later the systemic bone survey revealed a skull lesion, which was surgically removed. Two more years later, he had difficulty in opening mouth and was diagnosed to have a lesion at the mandible bone. Since then he was treated with PSL and bisphosphonate. Nevertheless, he complained of right sided lumbago two more years later due to the involvement of newly appeared iliac bone lesions. Currently the patient has had multiple bone lesions as well as CDI. He needed further systemic chemotherapy for active disease.

Case 11

A 53-year-old female first developed CDI at age of 41. Two years later, she was noted to have a right mandibular bone mass which was totally resected; however, diagnosis remained unknown. Three more years later she developed bone lesions at the frontal to left temporal skull, which caused a diffuse bone defect, including skull and facial bones (Figure 4C), when LCH was diagnosed. With systemic CT scan, she also was noted to have multiple osteolytic lesions at the skull, spine, scapula, rib and pelvis. She received LCH-A1 protocol[6], consisting of VBL and PSL for a year, which induced a new bone synthesis at the frontal bone. More recently, 12 years after the onset of initial symptoms, she has had newly-developed left mandibular osteolysis. She has currently been treated for active disease.

Case 12

A 36-year-old female was noted to have amenorrhea even after stopping milk feeding for her first-born baby. Administration of Gonadotropin-releasing hormone was successful in resuming a menstrual cycle and she gave birth of second child; however, soon after second childbirth she complained of symptoms compatible with CDI, when brain MRI showed a loss of bright spot at the pituitary posterior lobe; in addition, almost a year later, she was found to have a hypothalamic mass with a gadolinium (Gd)-enhanced MRI (Figure 5A). Biopsy of the mass confirmed the diagnosis of LCH. Since the probable compression of cerebrum due to a huge mass caused impaired consciousness, the patient received systemic chemotherapy, first with VBL followed by 2CDA.

Case 13

A 20-year-old girl first complained of polyuria/polydipsia and amenorrhea. Eight months later, she was detected a Gd-enhanced mass at the HPR by a brain MRI. An immediate open biopsy of the mass confirmed the diagnosis of LCH. Initially, irradiation (21 Gy) to the CNS markedly reduced the size of mass. Two years later, the patient was noted to have re-growth of hypothalamic mass, continued amenorrhea, poorly-controlled CDI and generalized cutaneous LCH, which was confirmed by

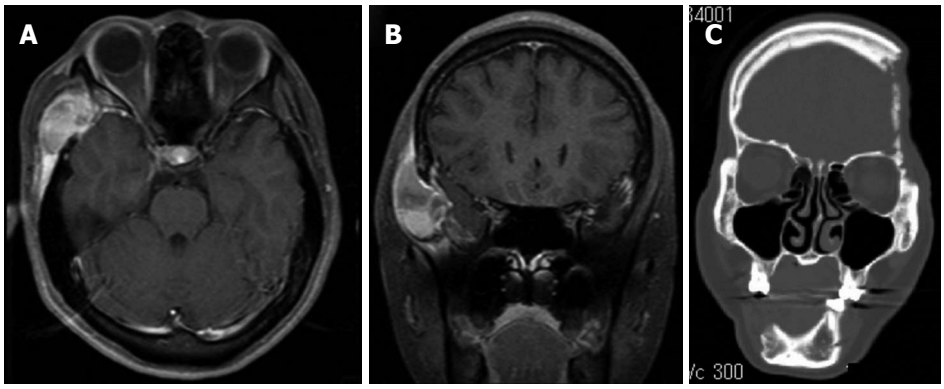

Figure 4 Langerhans cell histiocytosis skull mass (A, B) and lytic skull (C) lesion. A, B: Gadolinium-enhanced magnetic resonance imaging (T1W1) shows a mass with heterodensity at the right temporal area. axial view (A), coronal view (B); C: Computed tomography scan shows extensive lytic bones, at the left temporal bone and mandible. Defect of the right mandible is due to surgical resection.

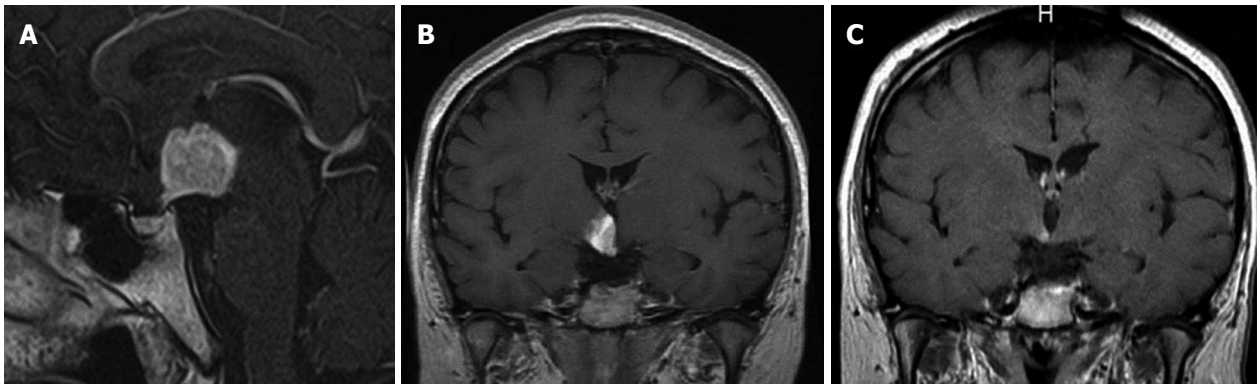

Figure 5 Langerhans cell histiocytosis mass at the hypothalamic area (A) and hypothalamic–pituitary area, comparison of pre and post chemotherapy (B, C). A: Gadolinium-enhanced magnetic resonance imaging (W1T1) shows a large mass at the hypothalamic area. Pituitary stalk is enlarged; B, C: Gadolinium-enhanced magnetic resonance imaging (T1W1) shows (B) a large mass before chemotherapy and (C) a residual mass post chemotherapy. The size of mass was significantly reduced after 2-deoxychloroadenosine treatment.

biopsy. Re-institution of systemic chemotherapy significantly (> 50%) reduced the size of hypothalamic mass. The patient has currently been in a state of ASAD.

Case 14

A 36-year-old female developed CDI in association with amenorrhea. However, the thickened pituitary stalk detected by MRI was put on under observation and not immediately treated. After progression of the thickened pituitary stalk into a significant Gd-enhanced mass at the HPR, a biopsy was performed to reveal typical LCH histology, when the patient had amenorrhea, fatty liver, reduced glucose tolerance. Systemic chemotherapy with 2CDA significantly (> 50%) reduced the mass size (Figure 5B and C). LCH lesions outside the CNS were not found. The patient remains markedly obese and diabetic, with residual active disease.

Case 15

A 38-year-old male was first diagnosed with primary hypothyroidism. Nineteen months later, he developed the symptoms of CDI, fatigue and disturbed consciousness along with disorientation and abnormal behaviors. A brain MRI revealed a Gd-enhanced mass at the HPR, which biopsy did not confirm the diagnosis of LCH. Two years later, osteolytic bone lesions appeared on the right femur and left clavicle, when the LCH was eventually diagnosed by a bone biopsy. The patient received systemic chemotherapy with 2CDA, but the mass size was reduced minimally (< 50%), and he remained significantly obese and diabetic. Four years from the initial CDI symptom, the patient developed retropharyngeal B-cell lymphoma. He has had active diseases of LCH as well as lymphoma.

Case 16

A 46-year-old male first presented with decreased libido and erectile dysfunction seven years after total gastrectomy for gastric adenocarcinoma. Four years later, a Gd-enhanced mass at the HPR was detected. Until then, he had ignored his polydipsia/polyuria symptoms, thus the diagnosis of CDI was delayed. Biopsy of the CNS mass led to a diagnosis of LCH. A systemic MRI survey also revealed multiple spinal involvements. The patient also had loss of concentration and short term memory deficits suggesting mild neurodegenerative disease, which findings were confirmed with brain MRI examination. Eventually, the patients received systemic chemotherapy

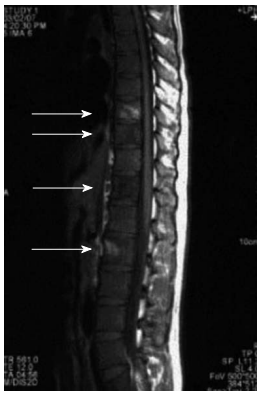

Figure 6 Langerhans cell histiocytosis spinal lesions. Non-enhanced magnetic resonance imaging (T1W1) shows high and low signals at multiple vertebral bodies (arrows).

with 2CDA, which markedly (> 50%) reduced the CNS mass size. However, currently, he has been treated for the regrowth of the CNS mass.

Case 17

A 23-year-old young adult was noted to have cerebellar ataxia and dysarthria. Past history revealed that at age of 16, he had been diagnosed as CDI; however, the exact cause was unidentified. At age 20, he was found to have polycystic lung disease with pneumothorax, followed by a mild ataxia. At age 23, he suffered a traffic accident when he was incidentally found to have a brain disease with a mass at the HPR as well as neurodegenerative disease on MRI performed at the emergency hospital. Eventually, LCH was diagnosed from the biopsy of lung tissues. He received monthly intravenous immunoglobulin therapy for neurodegenerative disease with dexamethasone[10]; however, the patient declined further treatment. Currently, he has remained with progressive neurological symptoms and with active lung disease.

Case 18

An 18-year-old man initially complained of low back pain and cervical mass. MRI revealed multiple spinal bone involvement (Figure 6). The initial diagnosis of LCH was made from the histology obtained by excisional iliac biopsy. A year later, he developed swelling of left cervical lymph nodes. CT scan of the chest also revealed a nodule in the right lung and the enlargement of left upper mediastinal lymph nodes. Histopathology of the biopsied cervical lymph node showed coexistence of two tumorous components; one was LCH and the other tissue of Hodgkin disease with Reed-Sternberg/Hodgkin cells being positive for CD30. The disease responded temporarily to irradiation (36 Gy) and systemic chemotherapy, but became refractory with relapses to the lungs and lymph nodes. Despite autologous followed by allogeneic HSCTs, he died of refractory Hodgkin disease at age of 23.

Summary of the cases

As summarized in Table 1, cases consisted of 3 SS-LCH (all CNS disease) and 15 MS-LCH. Regarding the initial symptoms, 7 (2 males and 5 females) of the 18 patients had CDI and other endocrine symptoms with thickened pituitary stalk or a mass at the HPR. Additional 2 patients initiated the disease with CDI with no immediate diagnosis. In the remaining patients, the disease begun with single (n = 3) or multiple (n = 1) spinal bone lesion(s) in 4 patients (all males), with multiple bone lesions in 3 patients (1 male and 2 females), with localized skull/muscle lesion in one female patient and with ambiguous symptoms including hypothyroidism in one male patient. Thyroid mass was noted in 2 patients. In terms of treatment, 9 patients received systemic immuno-chemotherapy alone, of whom 3 with CNS disease and 1 with multiple bone lesions received 2CDA. Five patients had a combination of immuno-chemotherapy with surgical resection or radiotherapy, 2 had immunotherapy alone, 2 had surgical resection followed by observation alone to date. Three patients received HSCT after extensive chemotherapy. In terms of outcome, 15 patients are alive (9 with active disease; AWAD, 6 without active disease; ASAD) with a median follow-up of 66 mo (range 17-166 mo) and 2 died of disease; 1 from sepsis-induced DIC and the other from progression of Hodgkin disease. The remaining 1 patient is lost to follow-up. As late sequelae, CDI (n = 9), neurodegenerative disease (n = 2) and obesity/diabetes mellitus (n = 3) are noted.

DISCUSSION

Clinical features

To date, adult LCH cases have mostly been reported as case series[14-18]. Here, we add another case series describing the clinical features and discussing the issues specifically relevant to adult LCH. Adult patients may have LCH as a recurrence of childhood LCH as well as *de novo* LCH developing first in adult life. Here described is all the latter type of LCH. None had a history of LCH in childhood.

Two major clinical features of non-pulmonary LCH in adults

It is apparent that there are two major groups; one is a CNS mass with endocrine problems (9/18) and the other is recalcitrant bone lesions (7/18). Both types of disease are histologically non-malignant, but extensive disease causes various impairments leading to the decreased quality of life, and limiting to achieve normal daily life activity.

Endocrine problems

Adult patients are often noted first with endocrine problems such as CDI, amenorrhea, loss of libido and obesity[9]. Particularly, hypothalamic-pituitary disease is the most common CNS manifestation of LCH, which leads to CDI and anterior pituitary hormone deficiencies. CDI is diagnosed from the finding that MRI scan shows absence of the bright spot of the posterior pituitary on

Table 1 Summary of 18 cases of non-pulmonary adult langerhans cell histiocytosis

Cases	Age (yr)/sex	Initial symptoms/signs	Subsequent symptoms/ disease progression	Treatment			Outcome	Follow-up (mo)
				Surgical resection	Radiation	Immune-chemo Rx/HSCT		
1	27/F	CDI/endocrine	None	Y	Y	Y[4]	LTF	-
2	25/F	CDI/endocrine	Nasal/thyroid/skin masses			Y	DOD[1]	216
3	35/F	MBL	MBL			Y/Y	ASAD	132+
4	37/M	CDI	MBL/skin lesions			Y/Y	ASAD	128+
5	40/M	MBL	MBL		Y	Y	ASAD	133+
6	46/F	Thyroid mass/spine (Th4)	MBL/LNs	Y		Y	AWAD	27+
7	40/M	Spine (C3)	Parietal bone	Y			ASAD	72+
8	40/M	Spine (C6)	Inguinal LNs			Y	AWAD	17+
9	27/F	Temporal bone	None	Y			ASAD	26+
10	31/M	Spine (Th1)	MBL			Y[4]	AWAD	108+
11	53/F	CDI	MBL	Y		Y	AWAD	166+
12	36/F	Endocrine	HPR mass			Y[3]	AWAD	28+
13	20/F	CDI/endocrine	Skin		Y	Y	ASAD	156+
14	36/F	CDI/endocrine	None			Y[3]	AWAD	52+
15	38/M	Hypothyroid	CDI/endocrine			Y[3]	AWAD	48+
16	46/M	Endocrine	CDI/MBL/ND-CNS			Y[3]	AWAD	60+
17	23/M	CDI	Lungs/ND-CNS			Y[4]	AWAD	72+
18	18/M	Spine (multiple)	LNs/Lungs		Y	Y/Y	DOD[2]	72

[1]From disseminated intravascular coagulation; [2]From Hodgkin disease; [3]Systemic chemotherapy with 2-deoxychloroadenosine; [4]Steroid alone with or without bisphosphonate. CDI: Central diabetes insipidus; MBL: Multiple bone lesions; HPR: Hypothalamic pituitary region; LNs: Lymph nodes; ND-CNS: Neurodegenerative central nervous system disease; Y: Yes; LTF: Lost to follow-up; ASAD: Alive without active disease; AWAD: Alive with active disease; DOD: Died of disease.

the T1-weighted sequences[9,19]; however, it is common that patients are taken care and followed up about these problems at the Endocrinology Unit until when Gd-enhanced MRI reveals a thickened pituitary stalk and/or a hypothalamic mass. Generally, it takes a year or longer for the mass to be biopsied and correct diagnosis be confirmed. Even when the diagnosis is confirmed, there are occasions that it takes time for the patient to be referred to hemato-oncologists for chemotherapy. Whenever the diagnosis and the introduction of treatment are delayed, the patient may develop not only endocrine problems but also cognitive impairment such as memory deficits as well as consciousness disturbances, as shown in our cases (Cases 12, 16, 17).

LCH in association with childbirth

The development of LCH in association with childbirth has not been well recognized. Regarding LCH occurring during pregnancy, only a few sporadic cases have been described previously[20,21]; however, no information is available how childbirth influenced on the development of LCH. In our series, the correlation between pregnancy/childbirth and LCH in adult female patients was noted in 4 cases (Cases 1-3, 12). Sex hormones are believed to participate in immune responses, as estrogens have been found to serve as enhancers in humoral immunity while androgens/progesterone appears to act as natural immune-suppressors[22]. For examples, postpartum thyroiditis/diabetes mellitus is speculated to be a consequence of the immunological flare that occurs after the lifting of the pregnancy-related immune suppression[23,24]. Moreover, pregnancy and the post-partum period are associated with increased breast cancer aggressiveness[25]. Thus, the hormonal imbalance in the postpartum period may trigger the development of LCH. Detailed examination of pregnancy and childbirth history in female LCH patients may clarify whether the associated hormonal changes influence the pathogenesis and the development of LCH.

LCH in association with various diseases/events

Two patients (Cases 16, 17) were noted to have cognitive disturbance due to LCH-related neurodegenerative CNS disease[10]. Additionally, two patients (Cases 15, 18) developed malignant lymphoma; one with concurrent LCH and Hodgkin disease and the other developed B-cell lymphoma after systemic chemotherapy for LCH. The association of LCH and other malignant lymphoid neoplasms has been well recognized[26-28]. In this series two patients (Cases 8, 9) with severe atopic dermatitis were found to develop LCH. This is an interesting topic considering the antigen-stimulation in the skin. It is also cautioned that recalcitrant or clinically atypical skin eruptions must be differentiated from LCH and other rare disorders[29] but no data is available that incidence of LCH is higher in patients with severe atopic dermatitis. Four patients (Cases 3, 5, 7, 8) were diagnosed to have LCH from spinal bone lesions. Particularly, of whom two had single spine (C3 or C6) involvement, not in the spinal body but in the arch. Spinal lesion should be searched for any adult who complained of cervical pain[30]. Intriguingly, discovery of LCH was triggered by road traffic accident in 2 patients (Cases 8, 17), although such reports are rarely found[31]. In Case 8, LCH lesion at the cervical spine was identified at the emergency hospital. In Case 17, traffic accident

incidentally led to the diagnosis of CNS- and pulmonary-LCH in the patient.

Importance of CT/MR/PET imaging for the diagnosis

To determine the precise biopsy/excision site of LCH, CT/MRI findings are inevitable. Particularly, bone scintigraphy for multiple bone lesions and Gd-enhanced MRI for CNS lesions are essential for the diagnosis of LCH[9,19]. However, more recently, ^{18}F-FDG PET is recommended. In one large study it was concluded that whole body FDG-PET scans can detect LCH activity and is useful to evaluate early response to therapy with greater accuracy than other imaging modalities (MRI, CT, plain films) in patients with LCH lesions in the bones and soft tissues[32]. Also, it is a useful tool for the monitoring of CNS disease activity in LCH[33,34]. It is said that ^{18}F-FDG PET might be useful to detect an early neurodegenerative lesions before MRI abnormalities appear, where bilateral hypometabolism is shown in the cerebellum and the basal ganglia (caudate nuclei) areas[34].

Therapeutic measures for adult LCH

In this case series, four patients received surgical resection of LCH mass without immuno-chemotherapy. Four patients received irradiation to the CNS-mass (n = 2), bone (n = 1) and lungs (n = 1), in association with immuno-chemotherapy. In the majority, systemic immuno-chemotherapy was given, mostly with a conventional combination of VBL/PSL or JCSL-96 protocol including VCR/cytosine arabinoside (AraC)/PSL[13] for induction. In 3 cases with CNS-LCH, 2CDA was employed. Previously proposed A1 protocol for adult LCH[6] was used only in one case in this series. With these measures, 6 ASAD cases were obtained, but necessity for further improvement of treatment for adult LCH seems apparent. As future trials, we have to scrutinize how efficiently we can employ AraC, 2CDA, clofarabine, and other novel agents for adult LCH patients. In the past, treatment reports on adult LCH cases were very limited[35,36]. In particular, the usefulness of intravenous 2CDA for CNS-LCH as well as for systemic MS-LCH was described in adult patients[37-40]. Windebank *et al*[41] also reported the usefulness of subcutaneous 2CDA treatment (5 mg/m^2 × 5 d, *sc*, q4 wk, for up to 6 cycles) in LCH. Effectiveness of the combination of 2CDA/AraC was described for extremely refractory cases[42]. More recently, effectiveness of clofarabine (25 mg/m^2 × 5 d, *iv*, q4 wk) has also been reported[43,44]. Particularly, Simko *et al*[44] demonstrated usefulness of clofarabine for multifocal skull lesions. On the other hand, Morimoto *et al*[11] reported the usefulness of Special C regimen of JLSG for treating adult LCH patients on ambulatory basis. Intriguingly, for the treatment of multiple bone LCH lesions in adults, Cantu *et al*[45] reported that AraC alone is an effective and minimally toxic, while VBL/PSL results in poor overall responses with excessive toxicity. Considering the fact that about 50% of LCH possess BRAF V600E mutation, molecular targetting treatment with vemurafenib has been proposed more recently[46]. As bone therapy regimen, Zoledronic acid as bisphosphonate is available, although its effectiveness on LCH bone lesions is still elusive[47]. Allogeneic HSCT for adult LCH is not within a scope of this article, although a few reports on pediatric LCH cases have been described[48,49]. As well recognized, in the recipients of allogeneic HSCT, care must be taken for the transplant related adverse events. In Table 2, a list of candidate systemic immuno-chemotherapy regimens is summarized, which we think is useful in choosing regimens for adult LCH patients. In practice, for an adult case of LCH with persistent minimal disease and systemic involvement, we prefer once a month or twice a month treatment, like Special C regimen of JLSG[11]. However, with these regimens, some adult patients may still show VBL neurotoxicity, MTX hepatotoxicity, or neutropenia due to mercatopurine hydrate (6MP); such events make it difficult to achieve the entire regimens as planned. Although we recognize that 2CDA is highly effective and could be useful in adult LCH, it is often difficult persuading the patients to stay in the hospital for the 5-d continuous treatment. If subcutaneous 2CDA is available at the outpatient care, this agent could be more employed in the treatment of adult LCH. In any case, it is important to make a most appropriate treatment plan for each patient individually. In summary, for adult patients with two major types of LCH, *i.e.*, recalcitrant multiple bone lesions and/or a mass at the HPR, early introduction of systemic immuno-chemotherapy using conventional regimens including AraC or alternative 2CDA or clofarabine regimens is recommended to overcome the disease-related impairment of qualify of life.

Table 2 Therapeutic options in the treatment of adult langerhans cell histiocytosis

Protocol	Drugs	Ref.
A1 protocol	VBL/PSL	[6]
JLSG-96	VCR/AraC/MTX/6MP/PSL	[13]
Cladribine-based	2CDA/PSL, 2CDA/AraC	[37-41]
Clofarabine-based	Clofarabine	[43,44]
JLSG-special C	VBL/MTX/6MP/PSL	[11]
Others	AraC alone	[45]
Molecular targetting	Vemurafenib	[46]
Bone therapy	Zoledronic acid	[47]

VBL: Vinblastine; PSL: Prednisolone; MTX: Methotrexate; 6MP: 6-mercatopurine hydrate; 2CDA: 2-deoxychloroadenosine.

ACKNOWLEDGEMENTS

The authors are grateful all the referring physicians; Drs. Noriharu Yagi (Ryukyu), Mahito Misawa (Hyogo), Eiichi Tanaka (Kumamoto), Masato Kohchi (Kumamoto), Hiroshi Kuroda (Kyoto), Hisashi Hatano (Nagoya), Takaaki Mizushima (Okayama), Katsuyuki Kiura (Okayama), Kiyomichi Hagiwara (Osaka), Shuichi Hanada (Kagoshima), Junichi Imamura (Kagoshima), Shiro Seto (Kishiwada), Kentaro Ohki (Chiba), Hisashi Wakiya (Chiba), Tsuguka

Shiwa (Hiroshima), Tetsuya Hiraiwa (Osaka), Atsushi Inagaki (Nagoya), Kento Hanyu (Tokyo). The authors also thank Ms. Michiko Amano (Japan LCH patients' association).

REFERENCES

1 **Egeler RM**, Annels NE, Hogendoorn PC. Langerhans cell histiocytosis: a pathologic combination of oncogenesis and immune dysregulation. *Pediatr Blood Cancer* 2004; **42**: 401-403 [PMID: 15049009 DOI: 10.1002/pbc.10464]

2 **Abla O**, Egeler RM, Weitzman S. Langerhans cell histiocytosis: Current concepts and treatments. *Cancer Treat Rev* 2010; **36**: 354-359 [PMID: 20188480 DOI: 10.1016/j.ctrv.2010.02.012]

3 **Badalian-Very G**, Vergilio JA, Degar BA, Rodriguez-Galindo C, Rollins BJ. Recent advances in the understanding of Langerhans cell histiocytosis. *Br J Haematol* 2012; **156**: 163-172 [PMID: 22017623 DOI: 10.1111/j.1365-2141.2011.08915.x]

4 **Imashuku S**, Ikushima S, Hibi S. Langerhans cell histiocytosis in adults in Japan. *Med Pediatr Oncol* 1998; **31**: 47

5 **Aricò M**, Girschikofsky M, Généreau T, Klersy C, McClain K, Grois N, Emile JF, Lukina E, De Juli E, Danesino C. Langerhans cell histiocytosis in adults. Report from the International Registry of the Histiocyte Society. *Eur J Cancer* 2003; **39**: 2341-2348 [PMID: 14556926]

6 **Arico M**, de Juli E, Genereau T, Saven A. Special aspects of Langerhans cell histiocytosis in adult. In: Weitzman S, Egeler RM, editors. Histiocytic Disorders of Children and Adults. Cambridge: Cambridge University Press, 2005: 174-186

7 **Vassallo R**, Ryu JH. Smoking-related interstitial lung diseases. *Clin Chest Med* 2012; **33**: 165-178 [PMID: 22365253 DOI: 10.1016/j.ccm.2004.04.005]

8 **Sundar KM**, Gosselin MV, Chung HL, Cahill BC. Pulmonary Langerhans cell histiocytosis: emerging concepts in pathobiology, radiology, and clinical evolution of disease. *Chest* 2003; **123**: 1673-1683 [PMID: 12740289 DOI: 10.1378/chest.123.5.1673]

9 **Imashuku S**, Kudo N, Kaneda S, Kuroda H, Shiwa T, Hiraiwa T, Inagaki A, Morimoto A. Treatment of patients with hypothalamic-pituitary lesions as adult-onset Langerhans cell histiocytosis. *Int J Hematol* 2011; **94**: 556-560 [PMID: 22015494 DOI: 10.1007/s12185-011-0955-z]

10 **Imashuku S**, Shioda Y, Kobayashi R, Hosoi G, Fujino H, Seto S, Wakita H, Oka A, Okazaki N, Fujita N, Minato T, Koike K, Tsunematsu Y, Morimoto A. Neurodegenerative central nervous system disease as late sequelae of Langerhans cell histiocytosis. Report from the Japan LCH Study Group. *Haematologica* 2008; **93**: 615-618 [PMID: 18287136 DOI: 10.3324/haematol.11827]

11 **Morimoto A**, Shimazaki C, Takahashi S, Yoshikawa K, Nishimura R, Wakita H, Kobayashi Y, Kanegane H, Tojo A, Imamura T, Imashuku S. Therapeutic outcome of multifocal Langerhans cell histiocytosis in adults treated with the Special C regimen formulated by the Japan LCH Study Group. *Int J Hematol* 2013; **97**: 103-108 [PMID: 23243004 DOI: 10.1007/s12185-012-1245-0]

12 **Hirasaki S**, Murakami K, Mizushima T, Koide N. Multifocal Langerhans cell histiocytosis in an adult. *Intern Med* 2012; **51**: 119-120 [PMID: 22214636 DOI: 10.2169/internalmedicine.51.6630]

13 **Morimoto A**, Ikushima S, Kinugawa N, Ishii E, Kohdera U, Sako M, Fujimoto J, Bessho F, Horibe K, Tsunematsu Y, Imashuku S. Improved outcome in the treatment of pediatric multifocal Langerhans cell histiocytosis: Results from the Japan Langerhans Cell Histiocytosis Study Group-96 protocol study. *Cancer* 2006; **107**: 613-619 [PMID: 16804933 DOI: 10.1002/cncr.21985]

14 **Kilpatrick SE**, Wenger DE, Gilchrist GS, Shives TC, Wollan PC, Unni KK. Langerhans' cell histiocytosis (histiocytosis X) of bone. A clinicopathologic analysis of 263 pediatric and adult cases. *Cancer* 1995; **76**: 2471-2484 [PMID: 8625073]

15 **Malpas JS**, Norton AJ. Langerhans cell histiocytosis in the adult. *Med Pediatr Oncol* 1996; **27**: 540-546 [PMID: 8888814]

16 **Baumgartner I**, von Hochstetter A, Baumert B, Luetolf U, Follath F. Langerhans'-cell histiocytosis in adults. *Med Pediatr Oncol* 1997; **28**: 9-14 [PMID: 8950330]

17 **Götz G**, Fichter J. Langerhans'-cell histiocytosis in 58 adults. *Eur J Med Res* 2004; **9**: 510-514 [PMID: 15649860]

18 **Giona F**, Caruso R, Testi AM, Moleti ML, Malagnino F, Martelli M, Ruco L, Giannetti GP, Annibali S, Mandelli F. Langerhans' cell histiocytosis in adults: a clinical and therapeutic analysis of 11 patients from a single institution. *Cancer* 1997; **80**: 1786-1791 [PMID: 9351548]

19 **Kaltsas GA**, Powles TB, Evanson J, Plowman PN, Drinkwater JE, Jenkins PJ, Monson JP, Besser GM, Grossman AB. Hypothalamo-pituitary abnormalities in adult patients with langerhans cell histiocytosis: clinical, endocrinological, and radiological features and response to treatment. *J Clin Endocrinol Metab* 2000; **85**: 1370-1376 [PMID: 10770168 DOI: 10.1210/jc.85.4.1370]

20 **DiMaggio LA**, Lippes HA, Lee RV. Histiocytosis X and pregnancy. *Obstet Gynecol* 1995; **85**: 806-809 [PMID: 7724119 DOI: 10.1016/0029-7844(94)00404-2]

21 **Gutiérrez Cruz O**, Careaga Benítez R. [Diabetes insipidus and pregnancy]. *Ginecol Obstet Mex* 2007; **75**: 224-229 [PMID: 17849803]

22 **Cutolo M**, Sulli A, Capellino S, Villaggio B, Montagna P, Seriolo B, Straub RH. Sex hormones influence on the immune system: basic and clinical aspects in autoimmunity. *Lupus* 2004; **13**: 635-638 [PMID: 15485092 DOI: 10.1191/0961203304lu1094oa]

23 **Terry AJ**, Hague WM. Postpartum thyroiditis. *Semin Perinatol* 1998; **22**: 497-502 [PMID: 9880119 DOI: 10.1016/S0146-0005(98)80029-3]

24 **Füchtenbusch M**, Ferber K, Standl E, Ziegler AG. Prediction of type 1 diabetes postpartum in patients with gestational diabetes mellitus by combined islet cell autoantibody screening: a prospective multicenter study. *Diabetes* 1997; **46**: 1459-1467 [PMID: 9287047]

25 **Mathelin C**, Annane K, Treisser A, Chenard MP, Tomasetto C, Bellocq JP, Rio MC. Pregnancy and post-partum breast cancer: a prospective study. *Anticancer Res* 2008; **28**: 2447-2452 [PMID: 18751433]

26 **Adu-Poku K**, Thomas DW, Khan MK, Holgate CS, Smith ME. Langerhans cell histiocytosis in sequential discordant lymphoma. *J Clin Pathol* 2005; **58**: 104-106 [PMID: 15623497 DOI: 10.1136/jcp.2003.015537]

27 **Shin MS**, Buchalter SE, Ho KJ. Langerhans' cell histiocytosis associated with Hodgkin's disease: a case report. *J Natl Med Assoc* 1994; **86**: 65-69 [PMID: 8151725]

28 **Naumann R**, Beuthien-Baumann B, Fischer R, Kittner T, Bredow J, Kropp J, Ockert D, Ehninger G. Simultaneous occurrence of Hodgkin's lymphoma and eosinophilic granuloma: a potential pitfall in positron emission tomography imaging. *Clin Lymphoma* 2002; **3**: 121-124 [PMID: 12435286 DOI: 10.3816/CLM.2002.n.019]

29 **Sires UI**, Mallory SB. Diaper dermatitis. How to treat and prevent. *Postgrad Med* 1995; **98**: 79-84, 86 [PMID: 7501582]

30 **Simanski C**, Bouillon B, Brockmann M, Tiling T. The Langerhans' cell histiocytosis (eosinophilic granuloma) of the cervical spine: a rare diagnosis of cervical pain. *Magn Reson Imaging* 2004; **22**: 589-594 [PMID: 15120180 DOI: 10.1016/j.mri.2004.01.006]

31 **Lee YS**, Kwon JT, Park YS. Eosinophilic granuloma presenting as an epidural hematoma and cyst. *J Korean Neurosurg Soc* 2008; **43**: 304-306 [PMID: 19096637 DOI: 10.3340/jkns.2008.43.6.304]

32 **Phillips M**, Allen C, Gerson P, McClain K. Comparison of

FDG-PET scans to conventional radiography and bone scans in management of Langerhans cell histiocytosis. *Pediatr Blood Cancer* 2009; **52**: 97-101 [PMID: 18951435 DOI: 10.1002/pbc.21782]

33 **Büchler T**, Cervinek L, Belohlavek O, Kantorova I, Mechl M, Nebesky T, Vorlicek J, Adam Z. Langerhans cell histiocytosis with central nervous system involvement: follow-up by FDG-PET during treatment with cladribine. *Pediatr Blood Cancer* 2005; **44**: 286-288 [PMID: 15481071 DOI: 10.1002/pbc.20175]

34 **Ribeiro MJ**, Idbaih A, Thomas C, Remy P, Martin-Duverneuil N, Samson Y, Donadieu J, Hoang-Xuan K. 18F-FDG PET in neurodegenerative Langerhans cell histiocytosis : results and potential interest for an early diagnosis of the disease. *J Neurol* 2008; **255**: 575-580 [PMID: 18227990 DOI: 10.1007/s00415-008-0751-8]

35 **McClain K**, Allen C, Ebrahim S. Review of histiocytosis treatment and neurotoxicity in adult patients. *Pediatr Blood Cancer* 2009; **53**: 696

36 **Derenzini E**, Fina MP, Stefoni V, Pellegrini C, Venturini F, Broccoli A, Gandolfi L, Pileri S, Fanti S, Lopci E, Castellucci P, Agostinelli C, Baccarani M, Zinzani PL. MACOP-B regimen in the treatment of adult Langerhans cell histiocytosis: experience on seven patients. *Ann Oncol* 2010; **21**: 1173-1178 [PMID: 19861578 DOI: 10.1093/annonc/mdp455]

37 **Saven A**, Burian C. Cladribine activity in adult langerhans-cell histiocytosis. *Blood* 1999; **93**: 4125-4130 [PMID: 10361109]

38 **Adam Z**, Szturz P, Duraš J, Pour L, Krejčí M, Rehák Z, Koukalová R, Navrátil M, Hájek R, Král Z, Mayer J. [Treatment of Langerhans cells histiocytosis by cladribin reached long-term complete remission in 9 out of 10 adult patients]. *Klin Onkol* 2012; **25**: 255-261 [PMID: 22920165]

39 **Weitzman S**, Braier J, Donadieu J, Egeler RM, Grois N, Ladisch S, Pötschger U, Webb D, Whitlock J, Arceci RJ. 2'-Chlorodeoxyadenosine (2-CdA) as salvage therapy for Langerhans cell histiocytosis (LCH). results of the LCH-S-98 protocol of the Histiocyte Society. *Pediatr Blood Cancer* 2009; **53**: 1271-1276 [PMID: 19731321 DOI: 10.1002/pbc.22229]

40 **Schini M**, Makras P, Kanakis G, Voulgarelis M, Kaltsas G. Cladribine therapy in adults with advanced Langerhans cell histiocytosis. *Leuk Lymphoma* 2012; Epub ahead of print [PMID: 23101752 DOI: 10.3109/10428194.2012.744454]

41 **Windebank K**, Bigley V, Zammit I, Haniffa M, Nanduri V, Collin M. Treatment of adult LCH with subcutaneous cladribine. 28th Annual meeting of the Histiocyte Society; London, United Kingdom. 2012: 38

42 **Bernard F**, Thomas C, Bertrand Y, Munzer M, Landman Parker J, Ouache M, Colin VM, Perel Y, Chastagner P, Vermylen C, Donadieu J. Multi-centre pilot study of 2-chlorodeoxyadenosine and cytosine arabinoside combined chemotherapy in refractory Langerhans cell histiocytosis with haematological dysfunction. *Eur J Cancer* 2005; **41**: 2682-2689 [PMID: 16291085 DOI: 10.1016/j.ejca.2005.02.007]

43 **Rodriguez-Galindo C**, Jeng M, Khuu P, McCarville MB, Jeha S. Clofarabine in refractory Langerhans cell histiocytosis. *Pediatr Blood Cancer* 2008; **51**: 703-706 [PMID: 18623218 DOI: 10.1002/pbc.21668]

44 **Simko S**, Allen C, Hicks J, McClain K. Clofarabine as salvage therapy in histiocytic disorders. 28th Annual meeting of the Histiocyte Society; London, United Kingdom. 2012: 31

45 **Cantu MA**, Lupo PJ, Bilgi M, Hicks MJ, Allen CE, McClain KL. Optimal therapy for adults with Langerhans cell histiocytosis bone lesions. *PLoS One* 2012; **7**: e43257 [PMID: 22916233 DOI: 10.1371/journal.pone.0043257]

46 **Haroche J**, Cohen-Aubart F, Emile JF, Arnaud L, Maksud P, Charlotte F, Cluzel P, Drier A, Hervier B, Benameur N, Besnard S, Donadieu J, Amoura Z. Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the BRAF V600E mutation. *Blood* 2013; **121**: 1495-1500 [PMID: 23258922 DOI: 10.1182/blood-2012-07-446286]

47 **Montella L**, Merola C, Merola G, Petillo L, Palmieri G. Zoledronic acid in treatment of bone lesions by Langerhans cell histiocytosis. *J Bone Miner Metab* 2009; **27**: 110-113 [PMID: 19018458 DOI: 10.1007/s00774-008-0001-2]

48 **Steiner M**, Matthes-Martin S, Attarbaschi A, Minkov M, Grois N, Unger E, Holter W, Vormoor J, Wawer A, Ouachee M, Woessmann W, Gadner H. Improved outcome of treatment-resistant high-risk Langerhans cell histiocytosis after allogeneic stem cell transplantation with reduced-intensity conditioning. *Bone Marrow Transplant* 2005; **36**: 215-225 [PMID: 15937510 DOI: 10.1038/sj.bmt.1705015]

49 **Kudo K**, Ohga S, Morimoto A, Ishida Y, Suzuki N, Hasegawa D, Nagatoshi Y, Kato S, Ishii E. Improved outcome of refractory Langerhans cell histiocytosis in children with hematopoietic stem cell transplantation in Japan. *Bone Marrow Transplant* 2010; **45**: 901-906 [PMID: 19767778 DOI: 10.1038/bmt.2009.245]

P- Reviewer Porrata LF **S- Editor** Zhai HH **L- Editor** A **E- Editor** Zheng XM

百世登
Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com