

Original Article

Pediatric liver failure with massive sinusoidal infiltration of histiocytes

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Histiocytic neoplasms, such as Langerhans cell histiocytosis (LCH) and disseminated juvenile xanthogranuloma (JXG), can involve the liver and sometimes cause liver failure. We aimed to classify non-LCH histiocytic proliferating disorders that do not exhibit typical disseminated JXG histology. We examined four pediatric patients who presented with liver failure and splenomegaly. Two patients with liver cirrhosis without cholestasis underwent liver transplantation (LT). The other two patients presented with giant cell hepatitis causing neonatal/infantile acute liver failure (ALF). The infantile ALF patient also underwent LT. Liver dysfunction developed after LT in all three transplant cases and the grafts exhibited massive sinusoidal infiltration of histiocytes with hemophagocytosis, similar to the native liver. The neonatal ALF patient was treated with an LCH-type chemotherapy regimen, and is alive and well at 18 months. Infiltrating histiocytes were positive for CD68 and CD163, and negative for CD1a, CD207, and S-100 protein. The BRAF V600E mutation was not present. Liver histological findings were not consistent with conventional disseminated JXG or LCH, although the histological findings in other organs overlapped those of well-known histiocytic neoplasms. The histological and immunohistochemical findings of infiltrating histiocytes suggest that these four cases constituted a disseminated JXG-like systemic disease.

Keywords: disseminated juvenile xanthogranuloma, pediatric liver failure, Langerhans cell histiocytosis, liver transplantation, chemotherapy

INTRODUCTION

Histiocytic neoplasms are derived from mononuclear phagocytes. In children, solitary dermal juvenile xanthogranuloma (JXG) is the most common histiocytic neoplasm. Macroscopically, JXG exhibits cutaneous nodular and papular lesions. Microscopically, JXG cells are small and oval (sometimes including spindle cells), with a round to oval nucleus and pink cytoplasm. Nuclear grooves are not observed, but Touton cells are often present. In JXG, the cells become progressively xanthomatous with time. Older, regressing lesions of the skin exhibit fibrosis or sometimes consist mainly of spindle cells.

Disseminated JXG is a rare disease, with a frequency in the range of 3.9–5% of JXG cases. The disease is characterized by the proliferation of histiocytes similar to those in

dermal JXG, and affects the lung, liver, spleen, lymph nodes, bone marrow, head, and neck, including the central nervous system.¹⁻³ Systemic forms that involve the liver and bone marrow have been treated by therapeutic regimes usually used for Langerhans cell histiocytosis (LCH). Disseminated JXG with liver involvement is histologically characterized by the enlargement of portal tracts with dense infiltration of foamy macrophages, but bile ducts are spared.

LCH is a well-known neoplasm occurring in childhood that most commonly presents with a lytic bone lesion eroding the cortex. Liver involvement in LCH is characterized by microscopic findings of periductal fibrosis. Bile ducts surrounded by Langerhans cells demonstrate degeneration and periductal fibrosis, which are consistent with sclerosing cholangitis.


We report four pediatric liver failure cases in which liver

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failure was suspected to be the result of massive sinusoidal infiltration of histiocytes, a finding that was not consistent with LCH or disseminated JXG. To investigate the etiology of liver failure, we examined the pathological features of these four patients who presented with liver failure and splenomegaly.

MATERIALS AND METHODS

Patients

Case 1: A girl aged 12 years and 3 months

The patient presented at 5 years old with hepatosplenomegaly and thrombocytopenia. A definite diagnosis was not made at that time. Congenital hepatic fibrosis (CHF) was suspected after liver biopsy at the age of six. The patient underwent living donor liver transplantation (LDLT) at the age of 7 years and 8 months because of liver dysfunction and portal hypertension. However, after LT, splenomegaly and thrombocytopenia gradually progressed, and splenectomy was performed when the patient was 9 years old. Approximately 3 years after LT, graft function deteriorated and thrombocytopenia persisted. At this time, hypoalbuminemia and ascites developed. Considering the histological similarities between native liver and graft biopsies, chemotherapy typically given to LCH patients was administered. After chemotherapy, the patient's general condition improved and ascites disappeared. She has been well for 1 year under chemotherapy. The patient had no skin lesion.

Case 2: A girl aged 6 years and 1 month

At the age of 1 year and 6 months, the patient developed hepatosplenomegaly and yellow papular skin lesions. Juvenile myelomonocytic leukemia (JMML) or autoimmune lymphoproliferative syndrome were suspected and bone marrow biopsy was performed; however, a definite diagnosis was not made at that time. When the patient was 3 years old, she presented with pancytopenia as a result of splenomegaly and splenectomy was performed. After splenectomy, pancytopenia improved, but her respiratory function gradually deteriorated. Liver biopsy was carried out and hepatopulmonary syndrome was suspected. LDLT was performed when the patient was 5 years and 10 months. However, she died 3 months after LDLT because of respiratory failure and graft failure. Autopsy was performed.

Case 3: A girl aged 3 years and 8 months

At the age of 2 months, the patient presented with acute liver failure (ALF) and underwent LDLT. After LT, mild liver dysfunction continued and splenomegaly progressed; liver graft enlargement was also noted. Thrombocytopenia, which resulted from hypersplenism, progressed, and splenectomy was performed when the patient was 2 years old. She had a history of skin tumors from infancy.

Case 4: A girl aged 1 year and 6 months

The patient was delivered prematurely at 34 weeks and 4

days, and fetal hydrops was identified before birth. She exhibited anemia, thrombocytopenia, and coagulopathy from birth. Hepatosplenomegaly and liver dysfunction with jaundice were also observed. Bone marrow aspiration and wedge biopsy of the liver were performed 5 weeks after birth, but a definite diagnosis was not made. The patient had a skin rash on the face and extremities at birth, and skin biopsy was performed 56 days after birth. LCH-type chemotherapy was effective, and coagulopathy, liver function, and splenomegaly improved.

None of these four patients had evidence of central nervous system symptoms, and bone lesions (mass lesions or osteolytic lesions) were not evident on radiographic examination.

METHODS

Resected liver and spleen samples, and skin, graft liver, and bone marrow biopsy specimens were fixed with formalin and embedded in paraffin. Sections with a thickness of 4 μ m were prepared on silanized slides, and stained with hematoxylin and eosin. Immunohistochemical staining was performed using a BOND-MAX stainer (Leica Biosystems, Nussloch, Germany). Antibodies against CD68 (clone KP-1, DAKO, CA, USA), CD163 (clone 10D6, Novocastra, Nussloch, Germany), CD1a (clone MTB-1, Novocastra, Nussloch, Germany), CD207 (clone DCGM4/122D5, Eurobio Scientific, Paris, France), S-100 protein (Rabbit polyclonal, Nichirei Biosciences, Tokyo, Japan), and cytokeratin 7 (clone OV-TL 12/30, DAKO, CA, USA) were used for immunohistochemical staining.

Skin biopsy specimens were kept as frozen sections and detection of the BRAF V600E mutation was carried out as previously described.⁴ Two experienced pathologists (R.I. and A.N.) carried out the pathological examinations.

All research protocols of this study were approved by the ethics committee of the National Center for Child Health and Development (approval numbers 466 and 1476). Informed consent was received for experimentation with human subjects and pathological materials were obtained in accordance with the Declaration of Helsinki.

RESULTS

Clinical findings

The clinical findings are summarized in Table 1.

Histological and immunohistochemical findings

The histological findings of resected organs and biopsy specimens are summarized in Table 2.

Case 1

The resected liver at LT exhibited liver cirrhosis without cholestasis. Ductal plate malformation was not observed in the resected liver and CHF was excluded because of the histological findings. There was no evidence of cholangitis.

Table 1. Clinical presentation, therapy, and outcome

Case		1	2	3	4
Onset		12-year 3-month-old girl 5 years old	6-year 1-month-old girl 1 year and 6 months old	3-year 8-month-old girl 2 months old	1-year 6-month-old girl Prenatal
Symptoms	Hepatomegaly	(+)	(+)	(+)	(+)
	Splenomegaly	(+)	(+)	(+)	(+)
	Thrombocytopenia	(+)	(+)	(+) after liver transplantation	(+)
Therapy	Skin lesion	(-)	(+) from infancy	(+) from infancy	(+) from birth
	Liver transplantation	7y 8m for liver cirrhosis	5y 10m for liver cirrhosis	2m for acute liver failure	(-)
	Splenectomy	9y 1m	3y	2y 2m	(-)
	Chemotherapy	11y after liver transplantation	(-)	(-)	(+)
Outcome		Alive, graft enlargement	Died	Alive, graft enlargement	Alive and well

Table 2. Histopathological findings of resected organs and biopsy specimens

Case		1	2	3	4
Skin	Juvenile xanthogranuloma	(-)	(+)	(+)	(+)
*Genetic findings	BRAF V600E	Not examined	(-)	(-)	(-)
Liver	Liver cirrhosis	(+), 1203 g	(+), 655 g	(-)	(-)
	Giant cell hepatitis	(-)	(-)	(+), 257 g	(+)
	Infiltration of histiocytes	(++), sinusoids	(++), sinusoids	(++), sinusoids	(++), sinusoids
Spleen	Hemophagocytosis	(+)	(+)	(-)	(-)
	Splenomegaly	(+), 1631 g	(+), 1569 g	(+), 984 g	(+), (splenectomy not performed)
Bone marrow	Infiltration of histiocytes	(+), foamy histiocytes (xanthoma cells)	(+++), foamy histiocytes (xanthoma cells)	(+), foamy histiocytes (xanthoma cells)	
	Extramedullary hematopoiesis	(-)	(-)	(++)	
	Cellularity	Hyperplastic marrow (myeloid and erythroid)	Hyperplastic marrow (erythroid)	Hyperplastic marrow (myeloid)	Inappropriate material
Graft	Hemophagocytosis	(+)	(++)	(+)	
	Blast	(-)	(-)	(-)	
Graft	Infiltration of histiocytes	(++), sinusoids	(++), sinusoids	(+), sinusoids	Liver transplantation
	Hemophagocytosis	(+)	(+)	(-)	not performed
	Fibrosis	(++), perisinusoidal	(+), perisinusoidal	(+), perisinusoidal	

*Genetic findings; performed using skin biopsy

Infiltration of many enlarged histiocytes was observed in the sinusoids; these histiocytes were CD68- and CD163-positive, and CD1a- and CD207-negative (Fig. 1a-d). Some histiocytes had evidence of hemophagocytosis.

The resected spleen was markedly enlarged (1631 g) and infiltrated by foamy histiocytes (xanthoma cells). Bone marrow biopsy carried out after splenectomy revealed hyperplastic change (myeloid and erythroid), but there was no evidence of monotonous proliferation of blasts.

Graft biopsy demonstrated mainly perisinusoidal fibrosis and infiltration of histiocytes with hemophagocytosis in the sinusoids (Fig. 1e-h).

Case 2

The resected spleen weighed 1569 g and infiltration by many foamy histiocytes (xanthoma cells) was observed (Fig. 2a, b). Bone marrow biopsy revealed erythroid hyperplasia, but there was no evidence of monotonous proliferation of blasts. The resected liver exhibited cirrhosis and many histiocytes infiltrated the sinusoids; these histiocytes were positive for CD68 and CD163, and negative for CD1a, CD207, and S-100 protein (Fig. 2c-f). There was no evidence of cholangitis or enlargement of the portal tracts with infiltration of histiocytes. Some histiocytes had evidence of hemo-

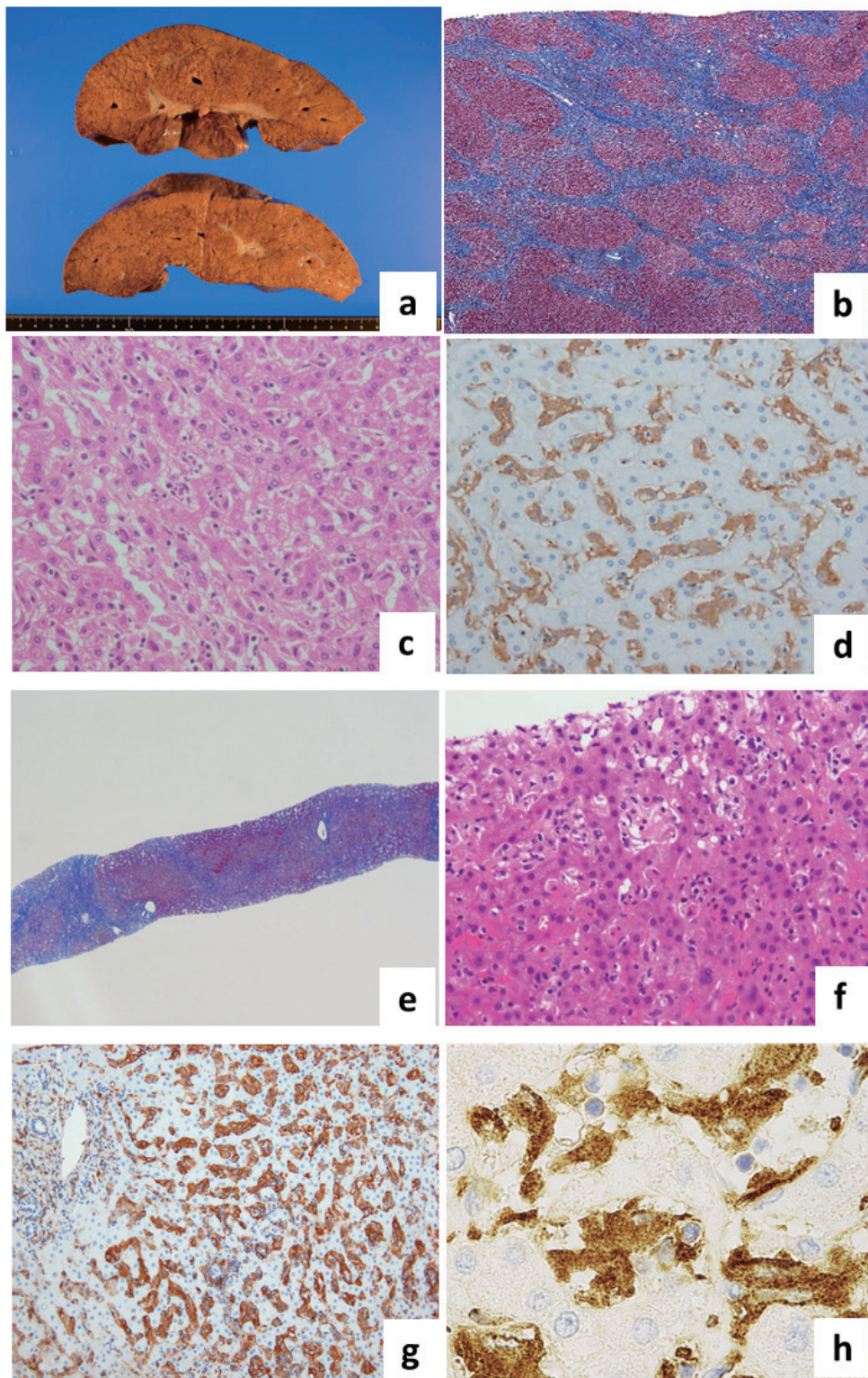


Fig. 1. Case 1: (a) Macroscopic appearance of the resected liver. The cut surface showed fibrosis but no cholestasis. (b) The resected liver showed cirrhosis (Masson-Trichrome staining $\times 40$). (c) Hematoxylin-eosin staining $\times 200$ and (d) immunohistochemical staining for CD163. Infiltration of histiocytes was seen in the liver sinusoids. (e) Graft liver biopsy 3 years after liver transplantation showed marked perisinusoidal fibrosis (Masson-Trichrome staining $\times 100$). (f) Hematoxylin-eosin staining $\times 200$ and (g, h) immunohistochemical staining for CD163. Infiltration of histiocytes was seen in the liver sinusoids, which resembled the native liver ($\times 200$ and $\times 1000$).

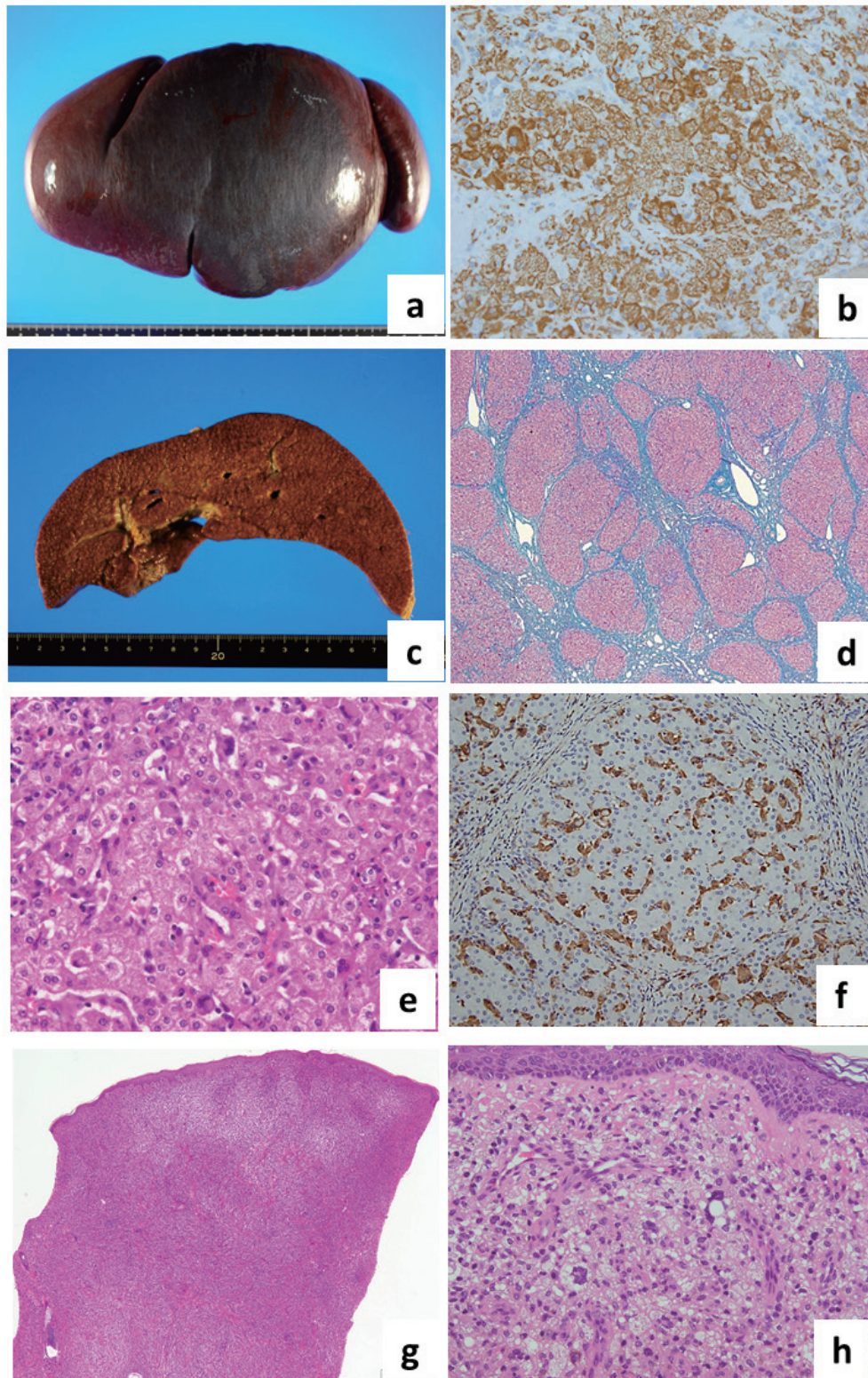


Fig. 2. Case 2: *(a)* Macroscopic appearance of the resected spleen. The spleen showed marked splenomegaly (1569 g). *(b)* Immunohistochemical staining for CD163. Infiltration of a large number of foamy histiocytes (xanthoma cells) was seen in the spleen. *(c)* Macroscopic appearance of the resected liver. The cut surface showed fibrosis but no cholestasis. *(d)* The resected liver showed cirrhosis (Masson-Trichrome staining). *(e)* Hematoxylin–eosin staining $\times 200$ and *(f)* immunohistochemical staining for CD163. Infiltration of histiocytes was seen in the liver sinusoids. *(g)* Low-power view of skin biopsy specimen showed infiltration of xanthoma cells in the dermis (hematoxylin–eosin staining $\times 40$). *(h)* Xanthoma cells and Touton giant cells were seen in the dermis (hematoxylin–eosin staining $\times 400$).

phagocytosis. Touton giant cells were not found. Skin biopsy demonstrated typical findings of dermal JXG (Fig. 2g, h).

Autopsy revealed the infiltration of large numbers of histiocytes in the liver, lymph nodes, accessory spleen, and bone marrow. Histiocytes that infiltrated the bone marrow had evidence of hemophagocytosis. The cause of death was considered to be multi-organ failure with the infiltration of histiocytes.

Case 3

The resected liver exhibited giant cell hepatitis. There was no evidence of enlargement of portal tracts with histiocytes; however, sinusoidal infiltration of many histiocytes and aggregation of histiocytes in the liver parenchyma were noted (Fig. 3a-e). These histiocytes were positive for CD68 and CD163, but negative for CD1a, CD207, S-100 protein, and lysozyme. Graft biopsy revealed extramedullary hematopoiesis and sinusoidal infiltration of histiocytes with perisinusoidal and perivenular fibrosis. The resected spleen exhibited marked extramedullary hematopoiesis and aggregation of foamy histiocytes (xanthoma cells). Bone marrow biopsy demonstrated marked myeloid hyperplasia with hemophagocytosis, but proliferation of monotonous blasts was not observed (Fig. 3f, g). Skin biopsy revealed typical dermal JXG with Touton giant cells (Fig. 3h).

Case 4

The liver biopsy specimen exhibited giant cell hepatitis, and many histiocytes, which infiltrated in the liver sinusoids, were CD68- and CD163-positive, and CD1a- and CD207-negative, but portal tracts were spared (Fig. 4a-d).

Biopsy of the skin rash on the patient's face provided evidence of dermal JXG (Fig. 4e-g).

Histiocytes infiltrating the liver in all four cases were positive for CD68 and CD163, and negative for CD1a, CD207, and S-100 protein. Moreover, sclerosing cholangitis, a characteristic histological feature of liver involvement in LCH, was not observed in any of the four cases.

Genetic findings

All three cases with dermal JXG had no BRAF V600E mutation (Cases 2, 3, and 4). As Case 1 had no skin lesions, BRAF V600E detection was not performed.

Whole-exome sequencing in Case 3 at the age of 2 years and 6 months revealed an activating *CBL* mutation. The patient was diagnosed with a Noonan syndrome-like phenotype with or without JMML,⁵ but has exhibited no signs of JMML thus far.

DISCUSSION

Emile *et al.* presented a revised classification of histiocytoses and neoplasms of the macrophage-dendritic lineage.⁶ This revised classification system consists of five groups of diseases: (1) Langerhans-related, (2) cutaneous and mucocutaneous, (3) malignant histiocytoses, (4) Rosai-Dorfman

disease, and (5) hemophagocytic lymphohistiocytosis and macrophage activation syndrome.⁶ It is currently difficult to categorize our cases using this revised classification. As infiltrating histiocytes in our cases were negative for CD1a, CD207, and S-100 protein, we were unable to categorize them into LCH group (1) or group (4). The infiltrating histiocytes/macrophages in the present series had a lower degree of cytological atypia and proliferation activity than those in malignant histiocytosis. Indeed, the Ki-67 labelling index of infiltrating histiocytes of our cases was not high (4-7%). The clinical findings in our cases did not fulfill the diagnostic criteria of hemophagocytic lymphohistiocytosis.⁷ Dermal JXG is included in group (2), whereas extracutaneous or disseminated JXG with *MAPK*-activating mutation or *ALK* translocations is classified into group (1).

The typical liver histology of conventional disseminated JXG is infiltration of tumor cells in the portal tracts. The livers in our four cases exhibited the infiltration of large numbers of histiocytes in the liver sinusoids, but not in the portal tracts. Consequently, liver histological findings were not consistent with conventional disseminated JXG. However, three of the four patients presented with dermal JXG. There have been several reports of disseminated JXG without concomitant skin lesions;^{2,3,8-10} therefore, the possibility of disseminated JXG was not able to be excluded in Case 1. Considering the systemic infiltration and immunophenotype of histiocytes, the findings in our four cases closely resembled those of disseminated JXG.

Although dermal JXG itself is a benign lesion, disseminated JXG, if not treated by chemotherapy, can result in death. Two patients (Cases 3 and 4) presented with ALF and were difficult to diagnose at the time of disease onset; consequently, it was difficult to determine the appropriate therapy. The presence of skin lesions is important for diagnosis in infants with ALF and hepatosplenomegaly. However, a case of neonatal disseminated JXG with delayed skin involvement has been reported.¹¹ Even if there are no skin lesions or skin lesions typical of dermal JXG at the time of disease onset, careful examination of the skin and skin biopsy is important to determine the best therapy.

There is a report of LT being performed in a neonatal case of disseminated JXG.¹² The patient survived for 28 months after LT, and neither recurrence in the graft liver nor liver dysfunction after LT was mentioned in the report.¹² All three of our patients who underwent LT (Cases 1, 2, and 3) exhibited enlargement of liver grafts, sinusoidal infiltration of histiocytes, and perisinusoidal fibrosis after LT. Our patients were not diagnosed with disseminated JXG at the time of LT and LT was necessary for the treatment of liver cirrhosis or ALF as a life-saving measure.

There have been reports of disseminated JXG being successfully treated by LCH-type chemotherapy regimens or other chemotherapy agents.¹³⁻¹⁵ After chemotherapy, one of our patients (Case 4) was alive and well at 18 months, and in Case 1, graft function improved after chemotherapy. Even if histological findings of liver biopsy specimens and clinical presentations are not initially typical of disseminated JXG, it

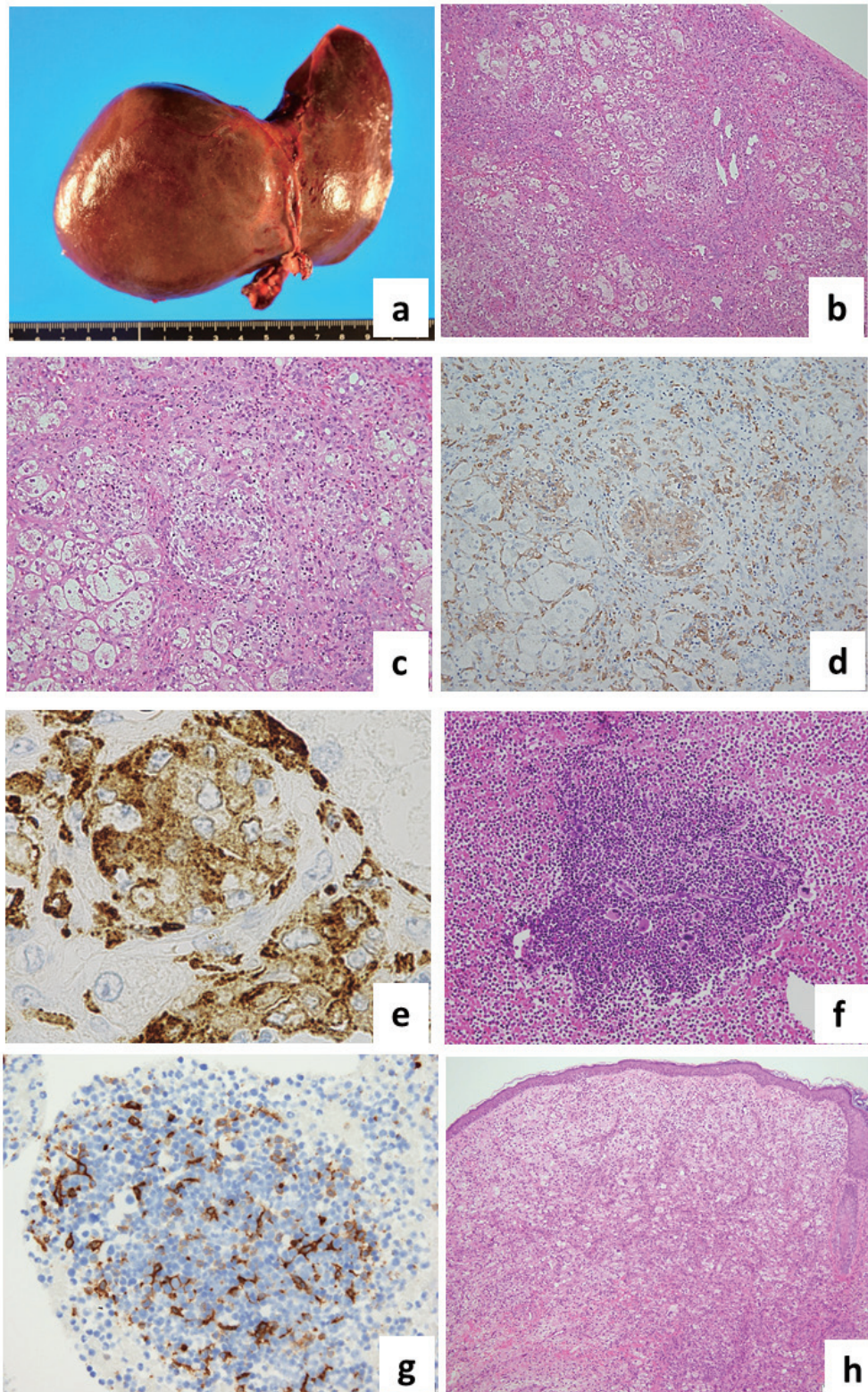


Fig. 3. Case 3: *(a)* Macroscopic appearance of the resected liver. The liver showed mild enlargement, but fibrosis was not conspicuous. *(b)* Microscopic appearance of the resected liver. Histological analysis identified giant cell hepatitis (hematoxylin–eosin staining $\times 100$). *(c)* Hematoxylin–eosin staining $\times 200$ and *(d, e)* immunohistochemical staining for CD163. Infiltration and aggregation of histiocytes were seen in the liver parenchyma ($\times 200$ and $\times 1000$). *(f)* Bone marrow biopsy after liver transplantation showed marked hypercellular marrow but no blast proliferation (hematoxylin–eosin staining $\times 200$). *(g)* Immunohistochemical staining for CD163. Infiltration of histiocytes was seen in the bone marrow, but the number of histiocytes was not marked and hemophagocytosis was absent. *(h)* Skin biopsy showed the infiltration of xanthoma cells and Touton giant cells in the dermis (hematoxylin–eosin stain $\times 100$).

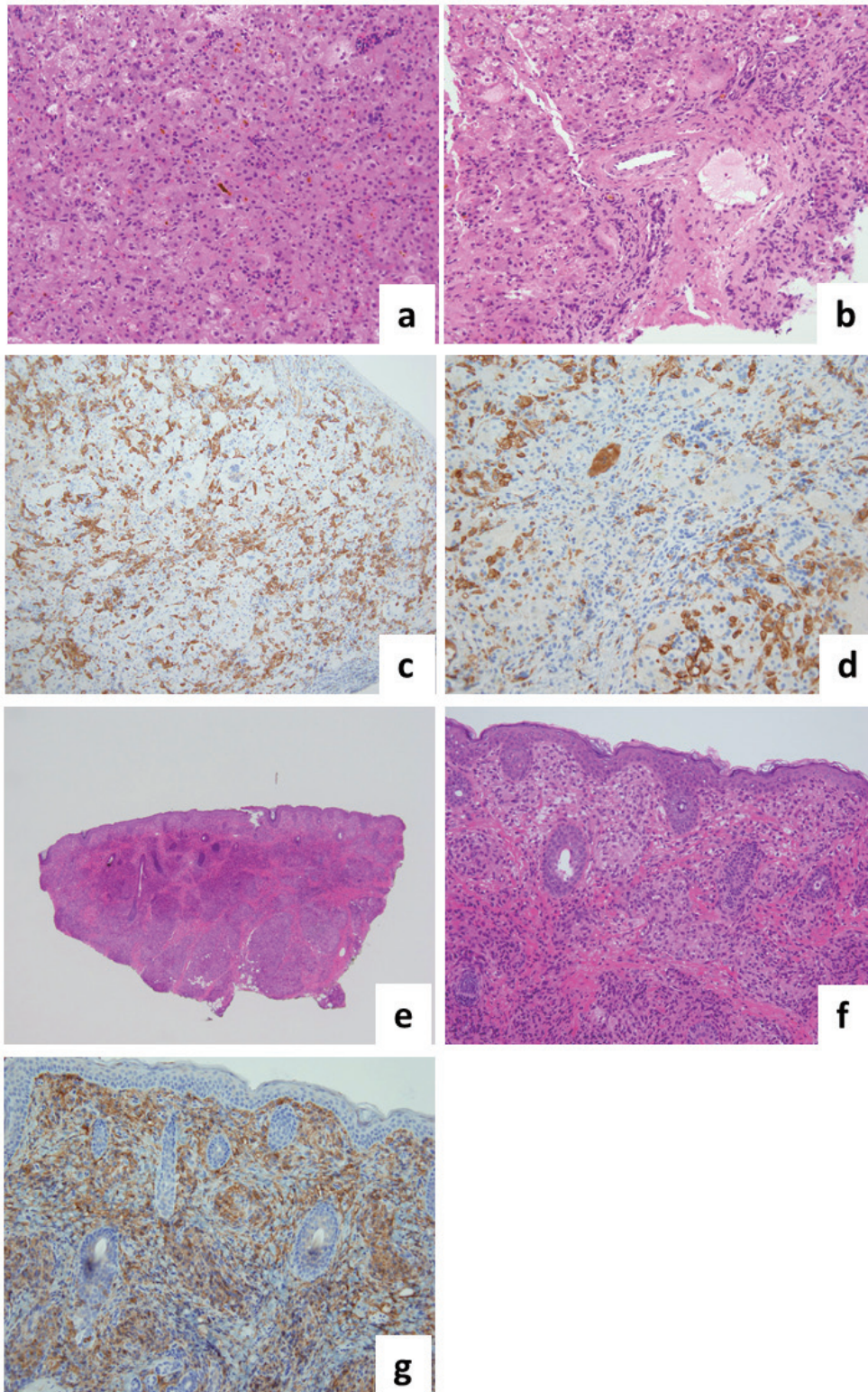


Fig. 4. Case 4: (a) Liver biopsy showed severe cholestasis and some hepatocytes showed giant cell transformation. (b) No enlargement of portal tracts with infiltration of histiocytes was seen. (c, d) Immunohistochemical staining for CD163. Infiltration of a large number of histiocytes in the liver parenchyma was seen, but only a few macrophages were found in the portal tracts (d). (e) Low-power view of skin biopsy specimen demonstrated a nodule-like lesion in the dermis (hematoxylin-eosin staining $\times 40$). (f, g) Skin biopsy showed infiltration of xanthoma cells in the dermis. (f) Hematoxylin-eosin staining $\times 200$ and (g) immunohistochemical staining for CD163.

is important to keep disseminated JXG-like systemic disease in mind as a potential differential diagnosis. This is especially true when encountering pediatric liver failure of unknown etiology with other symptoms such as splenomegaly, skin lesions, and bone marrow hyperplasia. We summarized the diagnostic flow chart and suggested therapy in liver failure cases with infiltration of histiocytes in Table 3.

Histiocytes in the liver are divided into two categories: Kupffer cells derived from embryonic progenitors from the yolk sac and monocyte-derived liver histiocytes originating from bone marrow.^{16,17} There are several markers for these two types of histiocytes, but it is difficult to clearly distinguish Kupffer cells from monocyte-derived liver histiocytes morphologically or using immunohistochemical staining in the human liver. Although distinguishing these two types of histiocytes is difficult, considering that massive infiltration of histiocytes was observed not only in the liver, but also in other organs, such as the spleen and bone marrow, we suspected monocyte-derived liver histiocytes as the cause of liver injury. Of note, Cases 1 and 2 developed liver cirrhosis of unknown etiology, which demonstrated marked sinusoidal fibrosis 2 and 4 years after the onset of disease, respectively. Recent studies revealed that hepatic stellate cells (HSCs) are the primary source of activated myofibroblasts, and several inflammatory and fibrogenic pathways function in their activation. Kupffer cells and bone marrow-derived monocytes promote HSC activation through cytokines such as transforming growth factor- β (TGF- β), platelet-derived growth factor (PDGF), interleukin-1 β (IL-1 β), and IL-17.¹⁸ Years of sinusoidal histiocytic infiltration may have induced continuous HSC activation, and caused the liver cirrhosis in Cases 1 and 2.

The BRAF V600E mutation has been detected in approximately 50% of LCH cases and in >50% of cases of Erdheim-Chester disease.¹⁹⁻²² Unlike for LCH and Erdheim-Chester disease, there are few reports of JXG patients having the BRAF V600E mutation.²³⁻²⁵ Analysis of skin biopsy

specimens in Cases 2, 3, and 4 revealed no BRAF V600E mutation. Histologically, these skin lesions were typical of dermal JXG, thus it was not surprising that no BRAF V600E mutations were found. Recently, Diamond *et al.* reported that MEK inhibition was effective for treating histiocytic neoplasms, which are characterized by marked dependence on mitogen-activated protein kinase (MAPK) signaling.²⁶ Durham *et al.* reported activating mutations in *CSF1R*, and rearrangements in *RET* and *ALK* in patients with histiocytosis.²⁷ They also reported that inhibitors of RET and ALK were effective against histiocytic neoplasms.²⁷ We examined BRAF V600E mutations only and all of our patients were negative. Further molecular and genetic markers are needed to facilitate the definite classification of these histiocytic disorders in the future. From now on, precise molecular examinations will be required to select the most suitable drug based on specific gene mutations in histiocytic neoplasms.

We presented four cases of pediatric liver failure with splenomegaly and dermal JXG. In each case, liver histology was not consistent with conventional disseminated JXG. However, taking into account the skin lesions and clinical course, we considered our patients to have disseminated JXG-like systemic disease. At present, the first treatment choice should be LCH-type chemotherapy to preserve life and avoid irreversible organ damage. However, when new specific molecular analysis becomes possible in the future, it is hoped that drugs can be more suitably selected in a case-by-case basis.

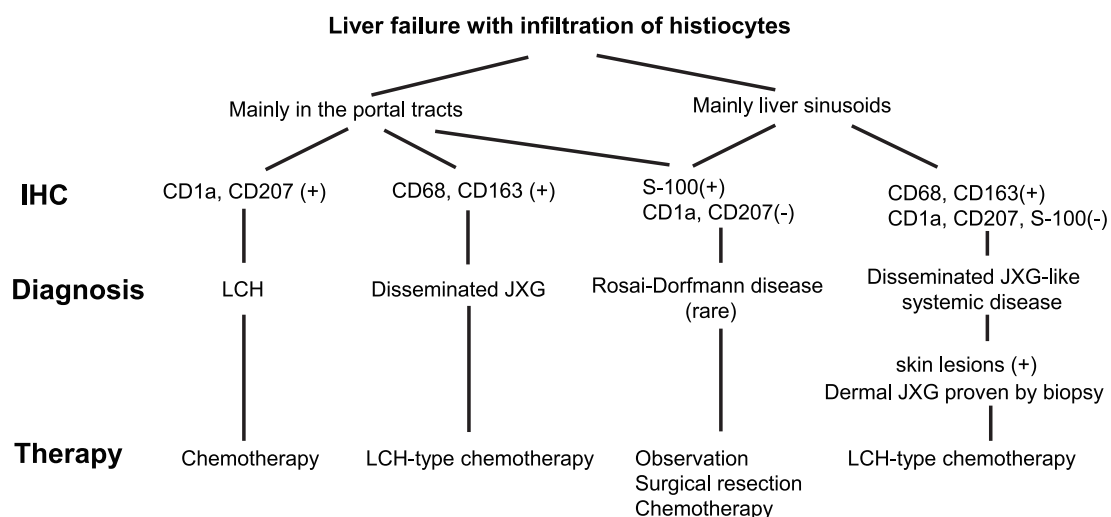
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AUTHORS' CONTRIBUTIONS

RI: study concept and design, data analysis, manuscript

Table 3. The diagnostic flow chart, suggested therapy in liver failure cases



IHC: Immunohistochemical staining, LCH: Langerhans cell histiocytosis, JXG: Juvenile xanthogranuloma

drafting, and obtaining funding; YS: study design, data analysis, and critical revision of the article for clinical content; TO, KS, MK, and KM: study design and critical revision of the article for clinical content; AN: study design, study supervision, and obtaining funding.

CONFLICT OF INTEREST

None

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