Clinical analysis of pediatric systemic juvenile xanthogranulomas: A retrospective single-center study

Hongyun Lian[1], Ang Wei[2], Lejian He[1], Ying Yang[2], Hong-hao Ma[2], Li-ping Zhang[2], Yitong Guan[1], Qing Zhang[1], Dong Wang[3], Zhigang Li[1], rui zhang[3], and Tianyou Wang[1]

[1]Beijing Children's Hospital
[2]Bejing Childrens Hospital
[3]Beijing Children's Hospital

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Abstract

Objective To investigate the clinical characteristics, treatment, and prognosis of children with systemic juvenile xanthogranuloma (JXG). Methods Children with JXG from January 2012 to December 2019 were retrospectively analyzed. Data relating to the clinical manifestations, laboratory values, treatment, and prognosis of the children were extracted from medical records. Patients underwent vindesine +prednisone as the first-line treatment and cytarabine + vindesine + dexamethasone +/- cladribine as the second-line treatment. Results Ten patients, including 8 males and 2 females, with an onset age of 1.95 (0.80-7.30) years, exhibited multi-system dysfunction. The median age of diagnosis was 2.45 (1.30-12.10) years. The most common location of extracutaneous lesions was the central nervous system (6 cases), followed by the lung (5 cases) and bone (4 cases). Nine patients underwent first-line chemotherapy, and 6 patients underwent second-line chemotherapy, including 5 patients with poorly controlled disease after first-line treatment. The median observation time was 20 (3-106) months. Nine patients survived, whereas one patient died of respiratory failure caused by pulmonary infection. By the end of follow-up, 7 patients were in an active disease (AD) state but better (AD-better), and 2 patients were in an AD-stable state. Three patients had permanent sequelae, mainly, central diabetes insipidus. The first-line treatment response rate was 40.0%, and the second-line treatment response rate was 66.7%. Conclusion The chemotherapy protocol for Langerhans cell histiocytosis (LCH) was effective for patients with systemic JXG, which also resulted in good outcomes. Central nervous system involvement did not impact overall survival, but serious permanent sequelae remained.

1 Introduction

Juvenile xanthogranuloma (JXG) is the most common non-Langerhans cell histiocytosis in children, and the incidence rate is approximately 1/1 000 000. Based on the different locations involved, it can be classified as cutaneous JXG and systemic (extracutaneous) JXG[1-2]. The most common presentation of JXG is a solitary cutaneous lesion. This type is self-limiting, and skin lesions can resolve spontaneously without treatment. Systemic JXG is rare, accounting for 4%-10% of JXG cases. Cases with visceral involvement or intracranial lesions are extremely rare. A subset of systemic JXG cases can also be self-limiting, but once the lesions invade the eye or the central nervous system, the prognosis is poor and may have sequelaes[3-4]. The treatment and prognosis, including late sequelae, of patients with systemic JXG remain unclear because the disease is so rare. Here, we report 10 cases of pediatric patients diagnosed with systemic JXG.

2 Patients and Methods

2.1 Patient

In all, children suffering from systemic JXG between January 2012 and December 2019 were enrolled in

this study. Data were retrospectively reviewed for the clinical manifestations, laboratory findings, age at onset, therapy, and prognosis. This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of Beijing Children's Hospital, Capital Medical University(2020-z-134). All patients' parents or guardians signed informed consent.

2.2 Diagnostic criteria

The inclusion criteria for a diagnosis of JXG in this study were as follows: characteristic Touton cells (rosette-like nuclei can be seen in the center; cytoplasm is eosinophilic or vacuolar) observed in biopsy, or immunohistochemical staining positive for Factor XIIIa, CD68, and/or CD163 and negative for Langerin and CD1a[5-6].

BRAF status was assessed either by DNA-based studies and/or immunohistochemistry with a clinically validated BRAF V600E (VE1) immunohistochemical stain.

2.3 Therapeutic regimens

Until now, there has been no unified or effective chemotherapy regimen for systemic JXG. Because both JXG and LCH are histiocytic diseases, our center utilizes a modified regimen based on the LCH-III and LCHS 2005 of the International Histiocyte Society to treat systemic JXG[6]. The details of the treatment elements are shown below. Due to the policy of our country, vinblastine was not be permitted to use. So, we used vindesine as the basis of treatment protocol.

2.3.1 First-line therapy

The following therapeutic regimen was implemented. For vindesine (VDS)+prednisone, the treatment stages were as follows: (1) initial induction treatment stage 1: VDS, 3 mg/m^2/dose, i.v. bolus, once a week for 6 weeks and prednisone (40 mg/m^2/day) administered orally at two divided doses on days 1-28, followed by gradual tapering for the following 2 weeks; (2) initial induction treatment stage 2: VDS, 3 mg/m^2/dose, i.v. bolus, once a week for 6 weeks and prednisone (40 mg/m^2/day) administered orally at two divided doses on days 1-3, weekly for 6 weeks; (3) maintenance treatment stage: VDS, 3 mg/m^2/dose, i.v. bolus, day 1 every 3 weeks, prednisone, 40 mg/m^2/day, orally, in two divided doses on days 1-5 every 3 weeks and 6-mercaptopurine (6-MP), 50 mg/m^2/day, orally, every night. The general duration of the course was 25 or 52 weeks.

2.3.2 Second-line therapy

Second-line therapy was initiated after discontinuation of first-line treatment (vindesine + prednisone) due to disease progression or as the initial treatment of patients with more severe conditions (such as liver, brain and lung involved). The second-line therapy was divided into two subgroups.

(A) Cytarabine + VDS + dexamethasone: cytarabine, 100 mg/m^2/day, i.v. gtt/h, days1-5; VDS, 3 mg/m^2/dose, i.v. bolus, day 1; and dexamethasone, 6 mg/m^2/day, i.v./oral, days 1-5. One cycle was twenty-one days, and after 8 cycles, patients entered the maintenance treatment stage.

(B) Cytarabine + VDS + dexamethasone + cladribine: cytarabine, 100 mg/m^2/day, i.v. gtt/h, days 1-5; VDS, 3 mg/m^2/dose, i.v. bolus, day 1; dexamethasone, 6 mg/m^2/day, i.v./oral, days 1-5; and cladribine, 5 mg/m^2/day, i.v. gtt/h, days 2-6. One cycle was 28 days, and after 4 cycles, the patients were switched to the protocol described in (A) for 4 cycles before entering the maintenance treatment stage.

Second-line maintenance treatment was the same as first-line treatment. The general duration of the second-line treatment was 1 year.

2.4 Evaluation of treatment

2.4.1 Evaluation time

The patients were evaluated at the 5th, 11th, 25th, and 52nd weeks during first-line chemotherapy. During the second-line treatment, the patients were evaluated every 4 cycles. During the maintenance treatment

stage, evaluations were carried out every 3 months. After drug withdrawal, evaluations were carried out at 3 months, 6 months, 1 year, 2 years, 3 years, and 5 years. For assessment of disease status, evaluation items included routine blood tests, biochemical tests, thyroid function tests, urine osmotic pressure tests, and imaging examinations (radiography, ultrasound, computed tomography, and/or magnetic resonance imaging of the involved location).

2.4.2 Evaluation of disease state

The disease state and treatment response of the patients were evaluated according to Histiocyte Society Evaluation and Treatment Guidelines 2009 for LCH[7-8]. Briefly, the disease states included nonactive disease (NAD) and active disease (AD). The treatment response was categorized as complete resolution (NAD), regression (AD-Better, AD-B), mixed (AD-Intermedia, AD-I), stable (AD-Stable, AD-S), and progression (AD-Worse, AD-W). The response rate (RR) was defined as the percentage of patients with AD-B among all patients. Event was defined as patient death and disease progression or recurrence.

2.5 Statistical Analysis

The statistical results are expressed as the median (range). Statistical analysis was performed by using IBM SPSS Statistics 24 software (IBM, USA). Skewed distribution data are presented as the median (quartile). Independent-samples t tests were used to test for differences in quantitative variables. The log-rank test was used to verify overall survival, and the log-rank test was used to compare the survival rate between different groups. $P<0.05$ indicated a significant difference.

3. Results

3.1 General patient information

Ten cases of systemic JXG were enrolled in this study, all these patients fulfilled the diagnostic guidelines, including 8 males and 2 females. The ratio of males to females was 4:1. The median age of disease onset was 1.95 (0.80-7.30) years. The median age of diagnosis was 2.45 (1.30-12.10) years. Children with central diabetes insipidus had a long interval between onset and diagnosis, the longest of which was 7 years (Table 1).

3.2 Clinical manifestations

The clinical manifestations of the patients varied. In the early stage of the disease, subcutaneous masses were the first manifestation in 3 cases (head mass in 1 case, limb mass in 2 cases) (cases 7, 8, 9) (Fig. 1), polydipsia and polyuria in 2 cases (cases 1, 10), abdominal distension in 2 cases (cases 2, 3), epilepsy in 1 case (case 5), simple rash in 1 case (case 6) and claudication in 1 case (case 4).

Skin lesions were observed in 6 cases, with most presenting scattered red or yellow nodules 0.5-1.0 cm diameter in diameter (Fig. 2). The locations of extracutaneous lesions were the central nervous system in 6 patients (four brain parenchyma, one pituitary, and one both brain parenchyma and pituitary) (Fig. 3), lung in 5 patients, bone in 4 patients, liver in 3 patients, eye in 2 patients, endocrine system in 2 patients (including the parotid, thyroid, testis, and pancreas glands), the hematological system in 2 patients and muscle in 1 patient (Table 1).

All children underwent etiology, biopsy, and flow cytometry of bone marrow to exclude other diseases, such as neurofibromatosis or juvenile myelomonocytic leukemia, which are commonly accompanied by JXG.

3.3 Pathological results

The diagnosis of JXG in all ten patients was made based on clinical presentation, histopathology, and immunohistochemistry. Three patients were diagnosed by biopsies of more than two organs. There were six biopsies in skin, 2 in bone, 2 in liver, and 1 each in brain tissue, muscle, testis, and bone marrow (Table 1). The diagnosis of JXG in lesions other than the biopsy sites was made by clinical manifestation, laboratory examination, imaging, or ophthalmic examinations.

Touton-type giant cells were present in 5 cases and foamy histiocytes were present in 3 cases. The immunohistochemistry results showed that all 10 patients were positive for CD68/CD163, Fascin and Factor XIIIa expression (Fig. 4). One patient was positive for S-100. The median value of Ki-67 was 10 (1-50)%. MPO were positive in 8 patients. Langerin and CD1a expression was negative in all 10 patients. Furthermore, 7 of the 10 patients (the remaining three patients had no data) were negative for the *BRAF V600E* and *PIK3* mutation in both tissue and plasma. Seven of the 10 patients (the remaining three patients had no data) had ALK rearrangement test, they all were negative.

3.4 Treatment and prognosis

All the patients received chemotherapy (Table 2). Among them, 9 patients received the first-line regimen at the initial treatment stage, including 1 patient (case 10) who accepted first-line treatment in other hospitals for 1 year. Due to his progression of the disease, this patient was admitted to our hospital for a second-line regimen (cytarabine + VDS + dexamethasone + cladribine). Of the 8 children who received first-line treatment in our hospital, 4 showed controlled and improved mitigation of their lesions. After 12 weeks of treatment, the evaluation result of case 1 was AD-B, but she was lost to follow-up. Three patients (cases 4, 6, and 7) had finished the chemotherapy course. Their evaluation results indicated AD-S until their last follow-up.

Six children were treated with second-line therapy, including 5 patients who were poorly controlled after first-line treatment. Three patients were evaluated as AD-I (cases 2, 3, 9), one patient was evaluated as AD-W (case 10) who developed lameness, and one patient was evaluated as AD-S (case 5) whose lung involvement did not improve. All five patients accepted cytarabine + VDS + dexamethasone + cladribine treatment. Another patient (case 8) was directly administered cytarabine + VDS + dexamethasone as the initial treatment due to the severity of the condition and involvement of multiple organs. During second-line treatment, one patient (case 3) died of myelosuppression with complications relating to severe pulmonary infection and respiratory failure. One patient (case 8) underwent liver transplantation after one course of chemotherapy due to liver involvement and serious complications (liver cirrhosis and liver failure) and is now alive. In case 2, after 2 cycles of treatment, the evaluation of disease condition was AD-S, but this patient did not come back to our hospital for additional treatment. The condition of the other 3 patients improved after second-line chemotherapy, and 1 patient (case 10) had finished the chemotherapy course for 6 months and survived without events.

The end of follow-up period was July 30, 2020. The median follow-up time was 20 (3-106) months. Among the enrolled patients, 8 patients survived, 1 patient died, and 1 patient was lost to follow-up (considering the disease condition in the patient and the improved pituitary gland imaging at the last follow-up, we believe that she was still alive and evaluated as AD-B). By the end of follow-up, two patients were evaluated as AD-S, and seven patients were evaluated as AD-B. The first-line treatment response rate was 40.0%, and the second-line treatment response rate was 66.7%. Among the 9 surviving patients, three had permanent sequelae. Case 1 had persistent central diabetes insipidus, case 8 had liver cirrhosis, and case 10 had movement disorders, central diabetes insipidus, diminution of vision and abnormal thyroid dysfunction. Upon comparison, the involvement of central nervous system showed no significant difference in the 5-year overall survival rate (100.0% vs. 75.0%, log-rank test,P =0.2207), and there was no significant difference in the 2-year event-free survival rate between the two groups (50.0% vs. 75.0%, log-rank test, P= 0.3636) (Fig. 5).

4. Discussion

JXG is a kind of non-Langerhans cell histiocytosis characterized by yellow papules in the skin. JXG typically occurs in infancy or early childhood, and the typical clinical manifestation is single or multiple yellowish-brown solid papules or nodules[1-2]. The most common areas affected are the face, neck, and upper torso. Although most cases of JXG only occur on the skin, it can also manifest in other systems[9]. JXG could also be associated with neurofibromatosis-1 (NF1) and juvenile myelomonocytic leukemia (JMML)[1]. However, articles about systemic JXG are rare, and most of them are single case reports.

In this study, we described the characteristics of 10 patients with systemic JXG, including 7 patients with

intracranial lesions. This retrospective observational study showed several results. 1) The incidence of systemic JXG was sex-specific, and the disease mainly occurred in boys (males to females = 4:1), which is consistent with previous international reports[10-11]. 2) In terms of the age of onset, it was previously reported that 15-20% of patients had lesions at birth and that more than 75% had lesions within their first year of life[12]. However, our study found that only 1 case of systemic JXG was less than 1 year old, children less than 2 years old accounted for 50%, and 2 cases were more than 6 years old, suggesting that systemic JXG could occur in older children, but most of them were under 2 years old. 3) In systemic JXG, the most common lesion location (excluding skin) was the central nervous system, especially the pituitary gland. The Histiocytosis Study Group of the Japanese Society of Pediatric Hematology/Oncology reported that the onset age of patients with intracranial lesions was older than that of patients without intracranial lesions[11]. However, our study found no difference in the age of onset, which might be related to the small sample size. However, this study found that children with central diabetes insipidus had a long interval from onset to diagnosis. It was suggested that in the early stage of the disease, the clinical manifestations may be atypical, resulting in delayed diagnosis and permanent sequelae.

The pathological features of JXG are as follows: clear boundary of the lesion, dense infiltration of many histiocytes in the tissue, and scattering of lymphocytes, plasma cells, and eosinophils. Foam cells, foreign body giant cells, and Touton giant cells could be seen in the mature stage. Immunohistochemistry showed positive staining for Factor XIIIa, CD68, CD163, vimentin and anti-CD4 and negative staining for Langerin and CD1a [12-13]. In our report, the specific immunohistochemical markers CD68/CD163 and Factor XIIIa were all positive, but the positive rate of Touton giant cells was only 50%. A previous report showed that typical Touton giant cells could be found in 85% of cases[12]. Therefore, the diagnosis of JXG should be based on immunohistochemistry.

LCH, JXG, and ECD are all histiocytoses; thus. how can a differential diagnosis be developed among them? The difference between LCH and JXG lies in immunohistochemistry, in which Langerin or CD1a staining is positive[14]. In a previous study, some JXG patients were positive for *BRAF V600E* mutations[3,15]. However, according to the new classification criteria, the family of JXG with ERK-pathway mutations are now classified within the "L" (Langerhans) group, which includes LCH and ECD [17]. But there was some conflict about the diagnostic criteria, Picarsic et al[16] propose a revised diagnostic algorithm for CNS-JXG that includes an initial morphologic diagnosis with a final integrated diagnosis after clinical-radiographic and molecular correlation, in order to identify cases of pediatric ECD. They advised long-term follow-up to determine if pediatric BRAF V600E positive CNS-JXG neoplasms were a distinct entity in the L-group histiocytosis category or represent an expanded pediatric spectrum of ECD. However, patients who had CNS-JXG did not show BRAF V600E positive, especially one patient who accepted brain biopsy.

For treatment, most skin lesions in childhood can disappear spontaneously within 3-6 years and do not require treatment. However, there is currently no unified protocol to treat systemic JXG, and the current treatment regimens include surgery, chemotherapy, radiotherapy, and immunosuppressant therapy [18]. In addition, some articles showed that hematopoietic stem cell transplantation could be used to treat refractory extracutaneous JXG[19-20]. As histiocytic diseases, LCH and JXG are caused by abnormal proliferation of dendritic cells. Previous reports showed that the regimen for treating LCH (corticosteroids and vincristine) could be used in the treatment of multisystem JXG, and patients could achieve quick relief[21-22]. Previous studies also indicated that cladribine combined with cytarabine could successfully treat patients with multi-system JXG[23-24]. Therefore, we used VDS + prednisone as the first-line treatment and cytarabine + VDS + dexamethasone +/- cladribine as the second-line treatment. By the end of follow-up, two patients were evaluated as AD-S, and seven patients were evaluated as AD-B. The first-line treatment response rate was 40.0%, and the second-line treatment response rate was 66.7%. It is suggested that the effect of first-line treatment of JXG with multisystem involvement was inadequate, and more than half of the children needed second-line treatment for disease control. Therefore, the condition of systemic JXG may be more serious, and the treatment should be adjusted based on the evaluation results. Chemotherapy with second-line treatment was intense, but this study showed that the children were generally tolerant, except for 1 patient with myelosuppression who died of severe infection.

A previous study found that the prognosis of systemic JXG was good, 75% of children could survive disease-free, and less than 10% of children may die[23-24]. In our study, 9 of the 10 children survived, except one who died of chemotherapy-related complications. The presence or absence of intracranial lesions did not affect the prognosis of children with systemic JVG but may leave permanent sequelae (such as central diabetes insipidus). In addition, eye involvement may also leave permanent sequelae (such diminution of vision).

5. Conclusion

In this study, we found that the clinical manifestations of systemic JXG were diverse and commonly identified the central nervous system. The LCH chemotherapy regimen was effective for systemic JXG. The prognosis of systemic JXG was good, but patients with intracranial lesions may develop permanent sequelae. The number of patients in this study was small, and there was no risk-related factor analysis. Thus, it is still necessary to expand the cohort to study the efficacy of drug treatment and related adverse reactions. The follow-up time needed will also further prolong the analysis of the long-term prognosis of systemic JXG.

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