

ORIGINAL ARTICLE

A case report of pediatric systemic juvenile xanthogranuloma

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Abstract

Background: Juvenile xanthogranuloma (JXG) is a rare disorder that belongs to the broad group of non-Langerhans cell histiocytosis. It is characterized by one or more nodules with predilection sites on the head, neck, and trunk, and lesions that may be several millimeters in diameter. These are reddish or yellowish benign papules or nodules that usually resolve spontaneously. The involvement of organs other than the skin is termed systemic juvenile xanthogranuloma (SJXG). The eye is the most frequent extracutaneous location of the JXG.

Case presentation: We report a case of SJXG in a male child, with onset in the second month of life. He presented with several nodules, approximately 5 mm in diameter and tan-orange in color, located on the head, face, and trunk. The nodules enlarged to 10 mm in diameter, and new lesions were found in the right eye, which resulted in spontaneous hyphema and secondary glaucoma without treatment. The pathological findings suggested that the nodule was of histiocytic origin, and immunohistochemical analysis resulted in the diagnosis of JXG. Chemotherapy based on the Langerhans cell histiocytosis (LCH) regimen resulted in a good prognosis.

Conclusion: SJXG has low morbidity, but is unpredictable, and rare and self-limited. Treatment is required for patients with extracutaneous involvement, who may have increased morbidity. The LCH-III protocol of the International Histiocyte Society is the most commonly used and effective chemotherapy regimen.

KEYWORDS

juvenile xanthogranuloma, systemic juvenile xanthogranuloma, treatment

Feifei Liu and Man Hu contributed equally to this work.

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INTRODUCTION

Juvenile xanthogranuloma (JXG) is a very rare non-Langerhans cell histiocytosis and is regarded as benign dendritic cell hyperplasia [1]. Depending on the organ involved, it can be divided into cutaneous and systemic (extracutaneous) types [2]. In the majority of children with JXG, the disease is limited to the skin, presenting with red or yellow nodules of 0.5–1.0 cm in diameter, single or several, often occurring on the face, neck, and trunk in infants and young children, which may subside spontaneously in a few months to a few years, and most patients do not require treatment [3]. Importantly, the disease involving ≥ 1 organ other than the skin is called systemic juvenile xanthogranuloma (SJXG), which accounts for approximately 4% of JXG [4]. The most common site of extracutaneous involvement is the eye, followed by the subcutaneous soft tissue/muscle, central nervous system (CNS), lungs, liver, and spleen. SJXG rarely resolves spontaneously, with a poor prognosis and a mortality rate of nearly 4% [5]. Misdiagnosis or overtreatment often occurs in clinical practice owing to lack of understanding [6]. Here, we report a child with SJXG involving the eyes and lungs.

CASE PRESENTATION

A 7-month-old male presented with several nodules on the head, face, and trunk. The nodules were first noted on the head at 2 months old, and about 0.5 cm \times 0.5 cm in size, slightly protruding out of the skin surface. Due to the lack of other symptoms, including itching, the child was not treated. The nodules increased and enlarged gradually to a size of approximately 1 cm \times 1 cm in diameter, and small nodules began to appear on the forehead, face, and trunk. The child was admitted to a hospital in Shanghai, where a pathologic examination revealed

Key points

Juvenile xanthogranuloma (JXG) is a rare disorder that belongs to non-Langerhans cell histiocytosis, and the systemic juvenile xanthogranuloma (SJXG) involves organs other than the skin. SJXG has higher mortality and usually requires aggressive treatment. In our case, it was found that the LCH-III protocol is an effective treatment option.

a subcutaneous mass (abdominal wall) of histiocytic origin, suggestive of JXG (multiple). It was recommended that the child should be closely observed and reexamined after 6 months. Since then, the number and size of the child's skin nodules further increased, and the largest nodule was approximately 2 cm \times 2 cm.

At the age of 5 months, the child presented to the ophthalmology clinic of our hospital with complaints of redness and watering of the right eye for a few days. The clinical findings in the right eye included an enlarged eyeball, residual blood pigments over the lens, fibrin membrane in the anterior chamber, and high intraocular pressure (27 mmHg). There was no evidence of any mass lesion in the eyeball, except for one in the conjunctiva. However, ultrasound biomicroscopy showed a generalized bumpy iris contour (Figure 1). The patient was treated conservatively (1% prednisolone acetate three times a day, 2% carteolol twice a day, 1% brinzolamide twice a day, and tropicamide twice a day). During the subsequent follow-up, intraocular pressure gradually decreased to normal, and no fresh bleeding appeared in the anterior chamber.

The child was born at 40 weeks' gestational age, without any abnormality or history of trauma at birth, and no family history of heritable disease.

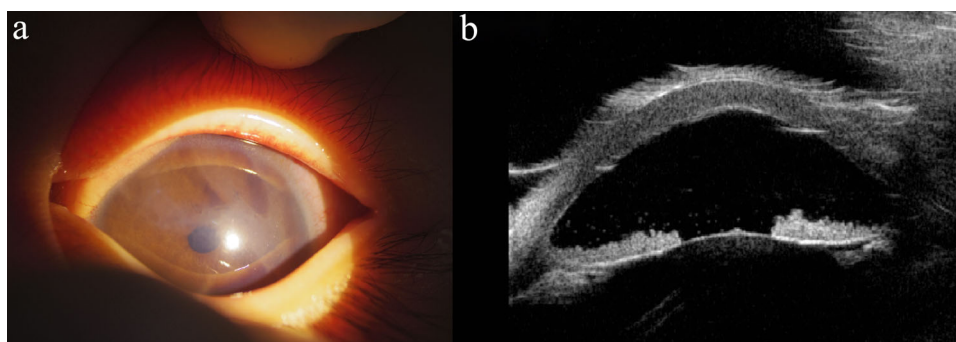


FIGURE 1 The clinical findings in the right eye. (a) Mass lesion in the eyeball. (b) Picture of ultrasound biomicroscopy.

Physical examination

Physical examination revealed the following vital signs: body temperature of 36.7°C, pulse rate of 145 times/min, respiration rate of 35 times/min, and body weight of 9.5 kg. The child exhibited normal development with good nutrition and a clear mind. There were nodules in the head, face, and trunk, with the largest being about 2 cm × 2 cm, protruding out of the skin surface (Figure 2), and the conjunctiva of the right eye was congested with visible secretion. Superficial lymph nodes were not palpable. Respiratory sounds were clear in both lungs, and the heart rhythm was synchronized with strong heart sounds. The abdomen was tender to palpation, there was no splenomegaly or hepatomegaly, and bowel sounds were normal. Neurological examination revealed no positive signs.

Ophthalmologic clinic

Ophthalmologic examination revealed an intraocular pressure of 27 mmHg in the right eye and 12 mmHg in the left eye. Examination of the right eye showed a yellowish mass on the nasal side of the bulbar conjunctiva, mild corneal edema with a horizontal corneal diameters of 12.5 mm, residual blood pigments over the lens, and fibrin membrane in the anterior chamber. Funduscopy showed mild pallor of the optic disc. In the left eye, the anterior and posterior segments were normal, except for mild pigmentation over the lens. Ultrasound biomicroscopy revealed a generalized bumpy iris contour and an anterior synechia in the right eye.

Pathological examination

Pathological examination of the skin nodules (abdominal wall) confirmed the diagnosis of JXG. Immunohistochemistry showed positivity for the cluster of differentiation antigen 63 (CD63) and CD163, weak focal positivity for Ki-67 protein (35%), and negativity for Langerin, CD1a, S-100, p63, CD117, and anaplastic lymphoma kinase (ALK).

Imaging findings: comprehensive radiological assessment of chest, cranium, and skeletal structures

Chest computed tomography (CT) results showed multiple subpleural nodular shadows in the lungs, low translucency in the dorsal aspect of both lungs, and localized subpleural cystic vesicular shadows. Cranial CT scans showed no abnormal signal in the brain parenchyma and multiple nodular abnormal signals



FIGURE 2 The skin nodules of the patient. (a, b) The nodules at the initial consultation. (c, d) The nodules after 11 weeks of treatment. (e, f) The nodules after 25 weeks of treatment.

in the fat layer of the scalp and soft tissues of the nose. Abdominal ultrasound and cardiac ultrasound showed no abnormality. X-ray examination revealed that the total spine, pelvis, and limb bones showed no abnormality.

Molecular diagnostics

Genetic testing showed that no causative or suspected gene mutations were identified. However, variations in

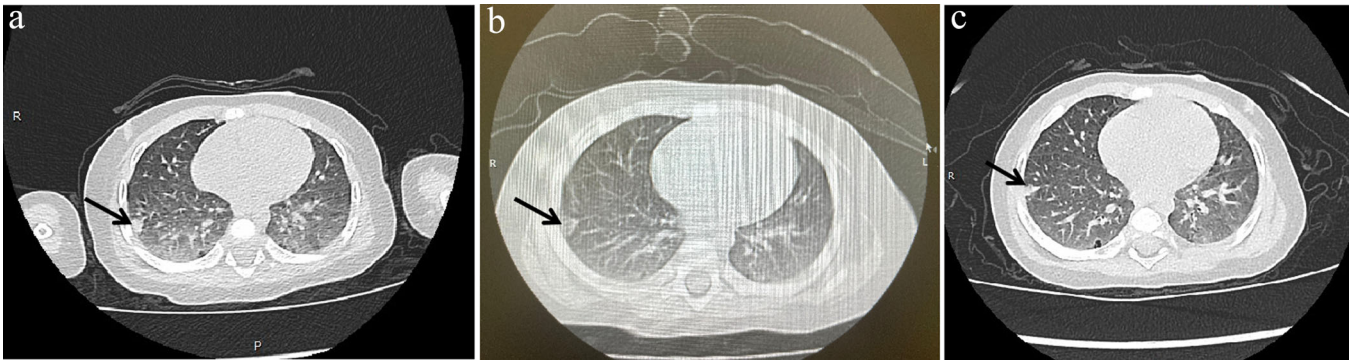


FIGURE 3 Imaging pictures of the lungs. (a) The lungs at the initial consultation. (b) The lungs after 11 weeks of treatment. (c) The lungs after 25 weeks of treatment.

SPEN and *CYBC1* were detected (*SPEN* location: Chr1:16263740, amino acid variation: c.10109C>Tp.P3370L; *CYBC1* location: Chr17:80402420, amino acid variation: c.343-345delGAGp.E115del), although the role of these variations in pathogenesis is currently uncertain and needs to be explored.

Treatment

Because there has been no international treatment protocol specifically for SJXG until now, the patient was treated with a modified regimen based on the LCH-III protocol of the International Histiocyte Society. The first-line therapy was a vindesine-prednisone combination treatment, beginning with a 12-week course of initial treatment (vincesine, 3 mg/(m²·day), once a week for 6 weeks; prednisone, 40 mg/(m²·day) orally, daily for 4 weeks after a weekly reduction for 2 weeks. The assessment in Week 5 was stable, so treatment was continued with vincesine, 3 mg/(m²·day), once a week for 6 weeks; prednisone, 40 mg/(m²·day) orally, Days 1–3, every 3 weeks). Maintenance therapy consisted of vindesine (3 mg/(m²·day) intravenous (IV) bolus, every 3 weeks) and prednisone (40 mg/(m²·day) orally, Days 1–5, every 3 weeks). The overall duration of the first-line therapy was 12 months. Simultaneously, the eye was treated by an ophthalmologist with prednisolone acetate.

Disease assessment was performed at weeks 11 and 25 of the first-line therapy, and showed a smaller rash and fewer lung nodules than before (Figure 2c–f; Figure 3). Intraocular pressure gradually decreased to normal, and no fresh bleeding appeared in the anterior chamber.

DISCUSSION

Histiocytoses are rare disorders characterized by the accumulation of macrophages, dendritic cells, or monocyte-derived cells in various tissues and organs,

and can be found in both children and adults. JXG, Langerhans cell histiocytosis (LCH), and Erdheim-Chester Disease (ECD) are common histiocytosis [7]. ECD and JXG are difficult to distinguish clinically and pathologically; however, over 60% of ECD patients have genetic mutations [8]. JXG and LCH often occur in infants and toddlers. ECD and LCH are considered inflammatory myeloid tumors and clonal diseases, whereas the cellular origin and pathogenesis of SJXG remain unclear [9]. JXG is prone to be complicated with juvenile myelomonocytic leukemia and neurofibromas [10]. The child did not exhibit this feature.

JXG was first reported in the early 1800s. 40%–70% of the cases develop within 1 year of age (within the first year of life). The male/female ratio of cutaneous JXG in children is approximately 1.4:1 [11]; however, there is no sex preference in adults. The incidence and etiology of this disease are unknown. This may be related to the abnormal reactive proliferation of mononuclear macrophages induced by infection or stimulation by physical factors, or it may involve a benign tumor reaction [12].

JXG is clinically rare and can be categorized into cutaneous and systemic types [13]. Skin-type lesions involve the skin and subcutaneous tissues, and are characterized by isolated reddish or yellowish-brown papules or nodules, which are mostly solitary. They can be found at birth in some patients, and are prevalent on the scalp, face, and trunk. The systemic type, also called the extracutaneous type, can involve the eye, internal organs, central nervous system, etc. The eye is the most common extracutaneous site of JXG, and children with multiple skin lesions and children under 2 years of age are at greater risk of ocular involvement [14]. The main feature of this case was multiple nodules on the skin all over the body, the rash gradually increased, and the lesions involved the eyes. Therefore, for cases with multiple skin lesions throughout the body, there should be a high alert for the involvement of other organs, such as the right eye, including enlarged eyeball, residual blood pigments over the lens, and a

fibrin membrane in the anterior chamber, as well as elevated intraocular pressure. There was one lesion in the conjunctiva. The diagnosis of SJXG was confirmed by a combination of clinical features, pathological diagnosis, and imaging. A skin biopsy provides a definitive clinical diagnosis [15]. Immunohistochemistry plays an important role in the differential diagnosis of LCH and JXG, which is positive for CD68, CD163, Ki-M1P, factor XIIIa, myofibrillar proteins, HLA-DR, CD4, and CD14, and, unlike LCH, is negative for S-100 and CD1a [16].

In our case, whole-exome sequencing was performed, and two mutation sites, *SPEN* and *CYBC1*, were identified. However, there are no research data showing that these two genes are related to the development of this disease. The *SPEN* gene is localized on chromosome 1, and diseases associated with *SPEN* include Radio-Tartaglia syndrome (RATARS) and chromosome 1p36 deletion syndrome (1p36DS). RATARS and 1p36DS are both neurodevelopmental disorders with similar clinical features, such as impaired intellectual development, speech delays, and behavioral abnormalities [17]. The *CYBC1* gene is located on chromosome 17, implicated in chronic granulomatous disease [18]. The clinical picture of chronic granulomatous disease is characterized by recurrent suppurative infections in various parts of the body, with granulomas formed by pigmented lipid-containing histiocytes in the affected organs. None of the above diseases have similar clinical manifestations to JXG [19].

JXG is a benign disease that is mostly self-limiting, with a small proportion of severe systemic damage requiring aggressive treatment. SJXG has higher morbidity and mortality rates than its cutaneous counterpart and usually requires aggressive treatment. Treatment includes surgical resection, local radiotherapy, and chemotherapy, but there is no standard treatment protocol. The LCH protocol is usually used, and if there is a causative genetic mutation, targeted therapy is given [3]. SJXG has a high likelihood of causing genomic alterations. Therefore, the patient received first-line systemic chemotherapy based on the LCH-III protocol [20]. In the present case of SJXG, the sites of involvement were the skin, eyes, and lungs. Patients with ocular involvement most commonly present with iris lesions, spontaneous hyphema, and secondary glaucoma. The iris lesion is treated with topical and/or periocular corticosteroids. Surgical management may be required if there is no response to intralesional steroids. The affected areas in this child were the skin, eyes, and lungs. The patient was treated with prednisolone. The intraocular pressure gradually decreased to normal, and there was no fresh bleeding in the anterior chamber. Simultaneously, the ophthalmologist applied steroids to treat the lesion and lowered the intraocular pressure with drugs. We learned

from this case that the LCH-III protocol for LCH is still the most effective treatment option available for JXG.

CONCLUSION

Children with multiple skin lesions, especially those under 2 years of age, should be aware of the risk of SJXG. Treatment is required for those with extracutaneous involvement. Chemotherapy based on the LCH regimen is associated with a good prognosis.

AUTHOR CONTRIBUTIONS

Feifei Liu, Man Hu, Rui Zhang, Zhigang Li, and Hongyun Lian wrote the manuscript.

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CONFLICT OF INTEREST STATEMENT

Professor Hongyun Lian is an Editorial Board member of *Malignancy Spectrum* and a coauthor of this article. To minimize bias, she was excluded from all editorial decisions making related to the acceptance of this article for publication. Peer review was handled independently by the other editors to minimize bias. The remaining authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Written informed consent was obtained from the guardian of the patient to publish this report in accordance with the journal's patient consent policy.

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