Case Report

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TANAFFOS

Congenital Skin Rashes in an IVF Baby Progressed to Multisystem Langerhans Cell Histiocytosis with Lung and Bone Involvement: A Case Report and Literature Review

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Langerhans cell histiocytosis is an uncommon proliferative disorder that may influence many organs; so, the clinical presentations vary.

Here we describe an 85-day-old female who was born with In vitro fertilization after 10 years of infertility. She referred to us due to severe pulmonary insufficiency and congenital progressive maculopapular rash with desquamation. There were significant cystic changes in chest imaging studies. Further evaluation demonstrated lytic lesions in cranial, femoral, and humorous bones. The skin biopsy verified the diagnosis of LCH.

A combination of Vinblastine, VP16, and Dexamethasone regimen was applied for the patient. In the course of the disease, she encountered multiple bilateral pneumothoraxes but didn't respond to tube thoracostomy and chemotherapy management. The patient died due to respiratory failure raised from complications of lung involvement as a multisystem LCH, 29 days later.

Pediatricians should pay much more attention to the cutaneous lesions in the neonatal period especially if there is any risk factor for presenting LCH such as IVF. The lesions should be monitored closely owing to a high correlation between skin lesions and MS LCH.

Keywords: Langerhans cell histiocytosis; In-vitro fertilization; Pulmonary involvement; Maculopapular rash; Multisystem LCH

INTRODUCTION

Langerhans cell histiocytosis is an uncommon disease identified with the infiltration of Langerhans cells in different organs. The incidence of LCH in children who are under 14 years old may be predicted to be about 4.1 per million people annually with an average age of 5.9 years at the time of diagnosis (1). The incidence of LCH in infants is even higher and is estimated as high as 15.1 per 1 million infants (2).

The clinical course of the disease varies from a self-limited and uni-focal osseous lesion to a fatal multiorgan disorder that affects pulmonary, hepatic, splenic, and hematopoietic systems(3). The multisystem variant of the disease frequently affects newborns and children, and

pulmonary association is rarely a main feature (4). Relative to adults in whom isolated pulmonary involvement is common, it is rare in children and chiefly presents as a part of the multiorgan disorder (5).

LCH should be diagnosed according to the clinical manifestations, histopathology, and imaging findings. The disease's prognosis depends on multiple parameters such as the affected organs, the age of onset, the severity of the organ dysfunction, and the disease progression (6).

Here we describe an 85-day-old female with skin rashes that appeared at birth which progressed to multisystem LCH with skin, lungs, and bone involvement. The informed consent was taken from her parents.

CASE SUMMARIES

An eighty-five-day-old female was referred to our hospital -which is a tertiary center in the capital of Iran- with the symptoms of fever, cough, tachypnea, shortness of breath and poor feeding started 4 days before. She had skin rashes on with her trunk, limbs, groins, diaper, and face since her birth. As the cutaneous lesions progressed to maculopapular rash, they were evaluated for TORCH and viral infections without any results to be concerned. Until the day of referral, she didn't have any difficulty in her breathing (no noisy breathing, tachypnea, cyanosis, or retractions).

She was born of non-consanguineous parents in the 38th gestational week of pregnancy with cesarean section delivery. She was a result of in vitro fertilization (IVF) pregnancy with a history of 10 years of infertility in her parents. Her mother had a history of 2 aborted fetuses. She had not been hospitalized before.

In the emergency ward, she had severe respiratory distress presented with suprasternal, intercostal, and subcostal retractions, tachypnea, and fever. She needed supplemental oxygen to maintain O_2 saturation within the normal range. Vital signs of the patient included respiratory rate: 68 breaths/min, pulse rate: 126 beats/min, temperature: 38.2°c, and blood pressure: 85/60 mm Hg. On auscultation, bilateral decreased lung sounds in addition to rales on the basis of the lungs were heard. Moreover, there were several vesiculo-papulo-macular lesions with desquamation on her face, trunk, groins, and extremities (Figure 1).

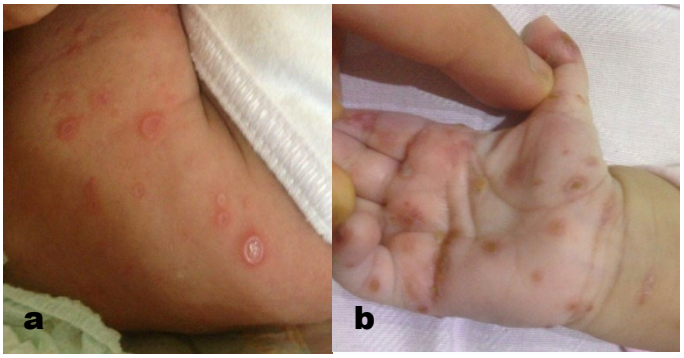

Figure 1. Maculopapular rashes of groin (a) and extremities (b) of an 85 days old female with multisystem LCH

Para clinical evaluation

Chest X-ray (CXR) revealed hyperinflation and diffuse bilateral reticular shadowing in the interstitium (Figure 2). Chest CT scan with contrast revealed bilateral multiple cystic lesions and diffuse septal thickening, suggestive of histiocytosis (Figure 3).

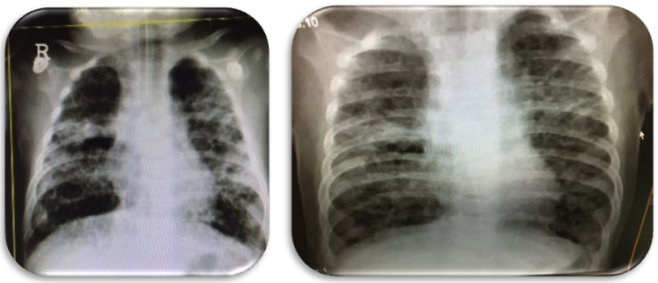

Figure 2. Chest radiograph after 3 months of her birth illustrates hyperinflation and diffuse interstitial reticular shadowing on both left and right sides

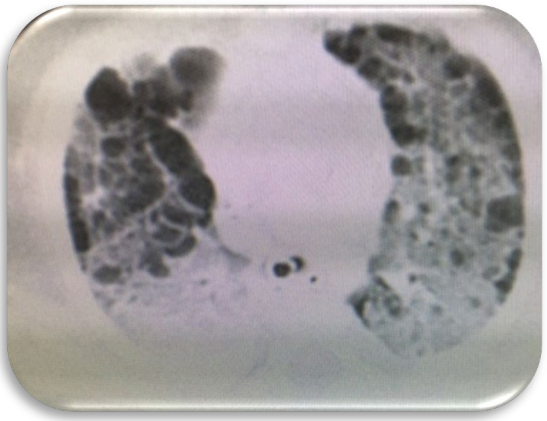

Figure 3. Axial chest CT with contrast show diffuse pulmonary cysts and nodules with intervening ground glass opacities.

Additionally, there were bilateral ground glass opacities in favor of superimposed infection. Further evaluations including skin biopsy, skeletal bone survey, abdominopelvic sonography, bone marrow aspiration, and biopsy (BMA & BMB), and echocardiography were performed. Histologic examination of the skin biopsy, aggregating to 0.5x0.4x0.1 cm showed dermal infiltration by mononuclear and a few multinuclear Langerhans cells, some with uniform grooved nuclei mixed with a few eosinophils and lymphocytes (Figure 4a). The cells were immunoreactive for S100 protein, CD1a (Figure 4b) and CD68. The diagnosis of Langerhans cell histiocytosis was made based on histologic and immunohistochemical findings. The skeletal bone survey revealed lytic lesions in the skull, femur, and humerus bones. Sonography demonstrated the normal size and echo patterns of the liver, spleen, and kidneys. BMA and BMB were normal. Echocardiography showed no significant abnormality.

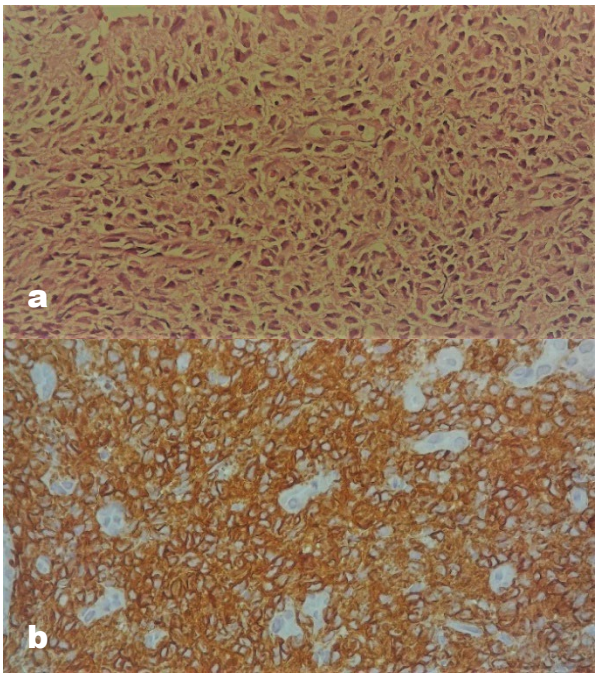

Figure 4. Dermal infiltration by mononuclear Langerhans cells (a). H&E, x400 IHC study for CD1a showed strong positivity in Langerhans cells (b). x400

Hospital course

She was admitted to the pediatric intensive care unit (PICU). Since her condition deteriorated, she was intubated and underwent mechanical ventilation. She was treated with wide-spectrum antibiotics including Meropenem, Vancomycin, and Co-trimoxazole. Furthermore, Acyclovir and Oseltamivir as antiviral agents and Amphotericin as antifungal agents were added to the treatment. As pathologic findings proved the LCH, she underwent Dexamethasone, Vinblastine, and VP16 treatment, but with a poor response. One day after the initiation of chemotherapy, she developed bilateral pneumothorax, at first on her right side requiring a chest tube along with a pneumothorax on the opposite side after 8 days. She was a candidate for pleurodesis, but her clinically unstable condition did not let us do that. Six days after initiation of chemotherapy, her white blood cells and platelet counts decreased to 800 and 54000 respectively. There was no improvement in respiratory manifestations as well as skin rashes. Her condition was consistently exacerbated. Unfortunately, she did not have a good response to the treatment and finally expired due to the inadequacy of pulmonary function raised from complications of pulmonary involvement of LCH after 29 days.

DISCUSSION

Langerhans cell histiocytosis appears with different presentations depending on which organ is involved. Several factors have been known to be associated with an increased risk of LCH including neonatal infections, thyroid disease, blood transfusions, feeding problems, and solvent exposure (7). Interestingly, in vitro fertilization has been also shown to be associated with a higher risk of LCH in children with a younger age at the time of diagnosis (8). However, the first manifestation of the present case who was conceived by IVF was skin involvement that appeared at birth. She had no sign of thyroid disease, neonatal infection, or blood transfusion before the admission. Thus, IVF would be the most probable predisposing factor for the occurrence of LCH in our patient.

The most common initial manifestation of LCH in children younger than 12 months is skin lesions. However,

the onset of manifestations since birth in LCH is rare (6). Interestingly, in a study evaluating children aged under 12 months with LCH, 24% of their patients presented at birth with the cutaneous involvement as the most common presentation (9). Skin rashes of our patient developed into an advanced disease with lung and bone involvement. Other studies have shown that multisystem involvements are more prevalent (about 41%) in children under 1 year old (9). Furthermore, there is an association between skin involvement and multisystem LCH (10).

Pulmonary involvement of LCH may appear with nonspecific clinical presentations including dyspnea, cough, chest pain, and fatigue, although 23% of patients with pulmonary LCH (PLCH) are asymptomatic (11). The presented case came to us for respiratory distress that suddenly happened 81 days after birth. She had progressive skin lesions since birth but was undiagnosed until pulmonary manifestation appeared. The median time from initial presentation to diagnosis of neonates with LCH is estimated at about 2 months (6). This case was diagnosed as LCH while respiratory manifestations appeared about 3 months after she was born.

Langerhans cell histiocytosis is classified into single-system disease and multisystem disease with at least two organ involvements. Each of them may divide into two subclasses, the former into single and multiple site forms and the latter into high and low risks forms. It is shown that almost all children with pulmonary LCH have multisystem LCH (3). Involvement of multiple organs such as the hematopoietic system, spleen, lung, and liver considered a high risk multisystem LCH (12). However, the lung as a risk organ has been excluded from a study by Ronceray et al. (13) as it did not affect survival. However, bilateral pulmonary involvement, in this case, was associated with a poor prognosis which may be due to potentially life-threatening events such as pneumothorax and respiratory failure resulted from the disease.

LCH can be diagnosed based on clinical presentation, imaging, and histopathological results. For a patient with a suspected LCH, further analyses like whole body skeletal survey, thoracic CT, bone marrow aspiration, sonography of the abdomen, and biopsy are recommended to distinguish between single-system and multisystem disease (14). Chest X-ray imaging and CT scan are key factors in the assessment of pulmonary involvement. High-resolution CT demonstrates specific features including peribronchial thickening, interstitial infiltrates, cysts, and nodules in the lungs (15). In the evaluation of our patient, all of the abovementioned were done. She had lung (multi-cystic lesions in CXR and CT), bone (lytic lesions in skull, femur, and humorous), and skin involvement but bone marrow, liver, and spleen were intact. Therefore, she is considered as multisystem LCH.

Biopsy of the lesions and immunohistochemistry of the specimen may show surface markers of the cell such as CD1a and S100, with CD1a being the more specific marker (14). However, immunohistochemistry staining of the skin biopsy of this case revealed CD1a and S100 antigens. Therefore, the diagnosis of the present case was confirmed as LCH. Lung parenchymal biopsy was not necessary due to the risk of pneumothoraxes in this patient with involvement of skin, bone, and lungs.

The prognosis of LCH depends on many parameters, such as the affected organs, the age of onset, the severity of organ malfunction, and the rate of disease progression (6). Mortality in high-risk multisystem LCH is of concern among the pediatric population and is estimated as high as 27% (16); so, management is challenging.

Isolated cutaneous LCH may be managed with the ''wait and watch'' approach, but close monitoring for disease progression is mandatory in such cases (6). However, for the treatment of multi-system LCH, several international protocols have been approved such as etoposide, glucocorticoids, cyclosporine, methotrexate, vinblastine, cyclophosphamide, cytarabine and doxorubicin. A combination of vinblastine and steroids is more common (17). The present case was treated with vinblastine, etoposide, and steroid, but she didn't respond to the regimen and her condition deteriorated. The complication of pneumothorax raised from multiple cystic

lesions of the lungs did not respond to chest tube insertion and chemotherapy, so she encountered with multiple pneumothoraxes episodes. Extensive cystic lung disease in LCH is a risk for life-threatening pneumothoraxes. They can be treated with pleurodesis, invasive surgical approaches with chest tubes, and chemotherapy (18). However, multiple bilateral pneumothoraxes in our case did not respond to tube thoracostomy and chemotherapy. Also, bilateral pulmonary involvement of LCH in a 3 y/o boy in another study did not respond to chemotherapy, chest drain, pleurodesis, and extracorporeal membranous oxygenation (ECMO) (19). She died from complications of the disease 29 days after admission.

CONCLUSION

LCH is an uncommon proliferative disorder with histiocyte-like cells which mainly affects children and has a poor prognosis at young ages. Pediatricians should pay much more attention to the cutaneous lesions in the neonatal period especially if there is any risk factor such as IVF for presenting LCH. The lesions should be monitored closely because there is a high correlation between skin lesions and MS LCH.

REFERENCES

1. Salotti JA, Nanduri V, Pearce MS, Parker L, Lynn R, Windebank KP. Incidence and clinical features of Langerhans cell histiocytosis in the UK and Ireland. ***Arch Dis Child*** 2009;94(5):376-80.
2. Guyot-Goubin A, Donadieu J, Barkaoui M, Bellec S, Thomas C, Clavel J. Descriptive epidemiology of childhood Langerhans cell histiocytosis in France, 2000-2004. ***Pediatr Blood Cancer*** 2008;51(1):71-5.
3. Abla O, Egeler RM, Weitzman S. Langerhans cell histiocytosis: Current concepts and treatments. ***Cancer Treat Rev*** 2010;36(4):354-9.
4. Barclay M, Devaney R, Bhatt JM. Paediatric pulmonary Langerhans cell histiocytosis. ***Breathe (Sheff)*** 2020;16(2):200003.
5. Nagy B, Soós G, Nagy K, Dezso B. Natural course of isolated pulmonary langerhans' cell histiocytosis in a toddler. 3-year follow-up. ***Respiration*** 2008;75(2):215-20.
6. Minkov M, Prosch H, Steiner M, Grois N, Pötschger U, Kaatsch P, et al. Langerhans cell histiocytosis in neonates. ***Pediatr Blood Cancer*** 2005;45(6):802-7.
7. Venkatramani R, Rosenberg S, Indramohan G, Jeng M, Jubran R. An exploratory epidemiological study of Langerhans cell histiocytosis. ***Pediatr Blood Cancer*** 2012;59(7):1324-6.
8. Akefeldt SO, Finnström O, Gavhed D, Henter JI. Langerhans cell histiocytosis in children born 1982-2005 after in vitro fertilization. ***Acta Paediatr*** 2012;101(11):1151-5.
9. Gargan ML, Wong JL, Leidhin CN, Owens C, Byrne A. Langerhans cell histiocytosis in children under 12 months of age: The spectrum of imaging and clinical findings: Experience in an Irish tertiary referral centre. ***Eur J Radiol*** 2021;134:109375.
10. Yi X, Han T, Zai H, Long X, Wang X, Li W. Liver involvement of Langerhans' cell histiocytosis in children. ***Int J Clin Exp Med*** 2015;8(5):7098-106.
11. Jezierska M, Stefanowicz J, Romanowicz G, Kosiak W, Lange M. Langerhans cell histiocytosis in children - a disease with many faces. Recent advances in pathogenesis, diagnostic examinations and treatment. ***Postepy Dermatol Alergol*** 2018;35(1):6-17.
12. Yağci B, Varan A, Cağlar M, Söylemezoğlu F, Sungur A, Orhan D, et al. Langerhans cell histiocytosis: retrospective analysis of 217 cases in a single center. ***Pediatr Hematol Oncol*** 2008;25(5):399-408.
13. Ronceray L, Pötschger U, Janka G, Gadner H, Minkov M; German Society for Pediatric Hematology and Oncology, Langerhans Cell Histiocytosis Study Group. Pulmonary involvement in pediatric-onset multisystem Langerhans cell histiocytosis: effect on course and outcome. ***J Pediatr*** 2012;161(1):129-33.e1-3.
14. Haupt R, Minkov M, Astigarraga I, Schäfer E, Nanduri V, Jubran R, et al. Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. ***Pediatr Blood Cancer*** 2013;60(2):175-84.

15. Lessick J, Abadi S, Agmon Y, Keidar Z, Carasso S, Aronson D, et al. Multidetector computed tomography predictors of late ventricular remodeling and function after acute myocardial infarction. ***Eur J Radiol*** 2012;81(10):2648-57.
16. Kim BE, Koh KN, Suh JK, Im HJ, Song JS, Lee JW, et al. Clinical features and treatment outcomes of Langerhans cell histiocytosis: a nationwide survey from Korea histiocytosis working party. ***J Pediatr Hematol Oncol*** 2014;36(2):125-33.
17. Zeller B, Storm-Mathisen I, Smevik B, Lie SO. Multisystem Langerhans-cell histiocytosis with life-threatening pulmonary involvement--good response to cyclosporine A. ***Med Pediatr Oncol*** 2000;35(4):438-42.
18. Eckstein OS, Nuchtern JG, Mallory GB, Guillerman RP, Musick MA, Barclay M, et al. Management of severe pulmonary Langerhans cell histiocytosis in children. ***Pediatr Pulmonol*** 2020;55(8):2074-81.
19. Soyer T, Özyüksel G, Türer ÖB, Çakmakkaya K, Yavuz S, Yalçın B, et al. Bilateral Pulmonary Langerhans's Cell Histiocytosis is Surgical Challenge in Children: A Case Report. European ***J Pediatr Surg Rep*** 2019;7(1):e8-e11.