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BRIEF REPORT
Multisystem Langerhans-Cell Histiocytosis With Life-Threatening Pulmonary Involvement—Good Response to Cyclosporine A

B. Zeller, MD,[1]* I. Storm-Mathisen, MD,[2] B. Smevik, MD,[3] S.O. Lie, MD, PhD[2]

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The treatment of multisystem Langerhans cell histiocytosis (LCH) in children under 2 years of age with organ dysfunction remains a challenge [1,2]. The current therapy includes corticosteroids, vinblastine (VBL), and etoposide (VP-16) [3]. In spite of such intensive chemotherapy regimens, about one-third of the patients in the poorest prognostic groups die [1] and there has not been a significant improvement in the last decade. Especially the group of patients not responding to the initial 6 weeks of treatment are at risk [4]. Different forms of salvage therapy have been tried, including thymic hormones and extracts, alfa-interferon, interleukin-2, and purine analogs [2]. From the beginning of the 1990s several reports on the efficacy of cyclosporine A (CSA) in the therapy of resistant LCH [5–9] were met with some enthusiasm. However, the encouraging initial results were not confirmed by more recent and larger studies [10–12]. We here report our experience with a girl with progressive, therapy-resistant multiorgan LCH that included extensive lung involvement, in whom the introduction of CSA changed the course of the disease and eventually led to a complete remission.

She was admitted at 4 months of age with respiratory distress, sweating, malaise and pallor. There was massive generalized lymph node enlargement, hepatosplenomegaly, and dyspnea. The respiratory rate was 80/min and there was intercostal and subcostal retractions. Chest X-ray films revealed multiple cystic structures together with infiltrates (Fig. 1).

A skeletal survey showed several punched-out osteolytic lesions in the skull, right humerus, and left tibia. The hemoglobin level was 8.7 g/dl, the leucocyte count 12.8×10^9/l, the platelet count 309×10^9/l. Lymph node biopsy confirmed the diagnosis of LCH as the biopsy stained positive for S-100 and anti-CD1a. Bone marrow aspiration revealed no Langerhans cells.

Treatment was started according to arm A of the LCH-2 protocol of the Histiocyte Society with daily steroids and VBL weekly. During the first week of therapy her respiratory problems progressed, and on day 7, she collapsed due to her first pneumothorax. Mechanical ventilation was needed thereafter. Treatment was switched on week 3 to arm B (VP-16 weekly in addition to prednisolone and VBL) because of progressing pulmonary involvement. The following weeks she developed multiple, large air-filled cysts in both lungs and suffered recurrent pneumothoraces. A total of 13 pleural drainages were performed over several weeks (Fig. 2); she had as many as five thoracic drains simultaneously.

Evaluation after 6 weeks of therapy according to LCH-2 protocol arm B revealed a mixed response: nearly complete resolution of the lymphadenopathy, but unchanged hepatosplenomegaly and progressive lung involvement, leaving the patient in a constantly life-threatening situation. Maintenance therapy (oral mercaptopurine, VBL and VP-16 every third week) was started. Steroids were continued at a lower dose. However, the patient's general and respiratory conditions were deteriorating so that at 11 weeks, the decision was made to stop conventional therapy and to change to the Histiocyte Society's salvage regimen, but omitting the anti-thymocyte globulin (ATG) that is included in that protocol. CSA was started at a dose of 12 mg/kg/day, aiming to maintain a plasma trough level of 150 to 200 ng/ml. Prednisolone was tapered and then continued at a low dose (0.1 mg/kg/day) for the next year.

There was an improvement in her condition during the first week of CSA therapy, and the respiratory situation stabilized. After 12 days on CSA, the last thoracic drain

[1]Department of Paediatrics, Central Hospital of Akershus, Oslo, Norway

[2]Department of Paediatrics, National Hospital of Norway, Oslo, Norway

[3]Department of Paediatric Radiology, National Hospital of Norway, Oslo, Norway

*Correspondence to: Bernward Zeller, Barneavdelingen, Sentralsykehuset i Akershus, N-1474 Nordbyhagen, Norway.
E-mail: bem.zeller@ah.telia.no

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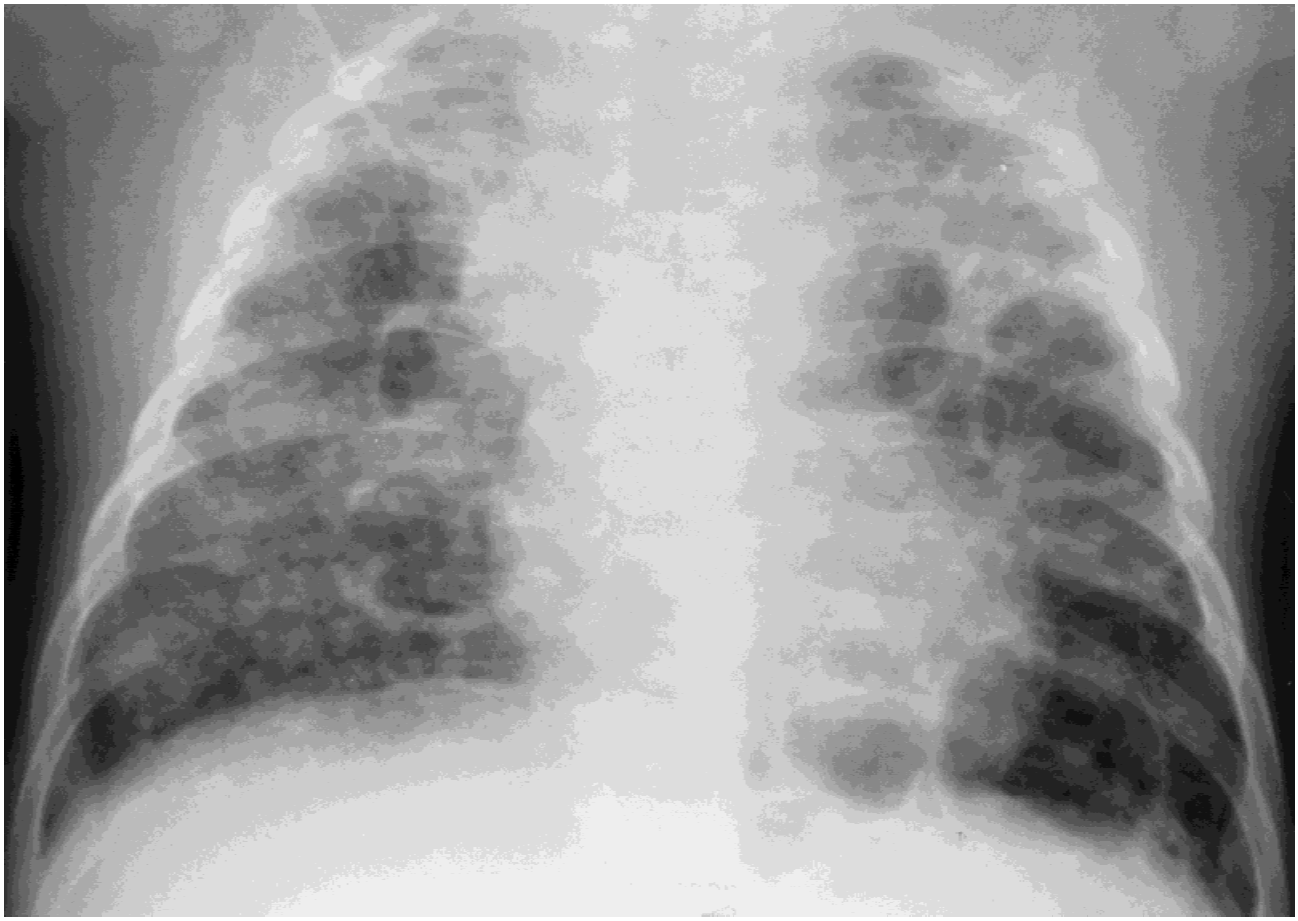

Fig. 1. Age 4 months. Chest radiograph shows cystic lesions in middle and lower lung fields bilaterally, as well as volume loss and opacities in both upper lobes.

was removed, and the respirator settings could also be reduced. Chest radiography at 6½ months of age still showed extensive bullae in both lungs (Fig. 3); and high-resolution CT 1 month later documented some improvement in the right upper lobe. Restitution of the lung parenchyma was a prolonged process. The girl required mechanical ventilation for 14 months, followed by 1 month with nocturnal continuous positive airway pressure (CPAP). Mild diabetes insipidus, treated by nasal desmopressine, developed during the 9th month of CSA therapy, and a rising erythrocyte sedimentation rate was interpreted as a possible sign of increased disease activity. At this point, it was decided to add oral mercaptopurine and methotrexate to CSA and prednisolone; the last was stopped after 12 months of CSA therapy. Mercaptopurine and methotrexate treatment was uncomplicated and continued until the age of 33 months when the CSA dose was reduced to maintain a plasma level of 100–150 ng/ml. Four months thereafter, she suffered a local relapse (single bone lesion in the forehead) that was treated successfully by intralesional steroids.

Chest radiography (Fig. 4), and CT of the lungs at the age of 2 years 8 months shows a high degree of restoration of functioning lung parenchyma. She is now, at 4 years of age, continuously on CSA. Her psychomotoric and social development has been normal and there are no signs of LCH activity. She has no signs of respiratory impairment and her length- and weight development is normal.

DISCUSSION

When CSA was started, the prognosis for our patient was extremely poor. She was under 6 months of age, had multisystem LCH with serious respiratory failure, and conventional therapy had failed to stop progressive lung involvement. The clinical condition improved immediately after starting CSA. No new pneumothoraces were observed and she could eventually be taken off artificial ventilation. Was this an effect of CSA? This is strongly suggested by the immediate improvement following the start of CSA therapy and the lack of beneficial effect of the preceding treatment. We have now treated our patient for more than 3½ years, to our knowledge the longest

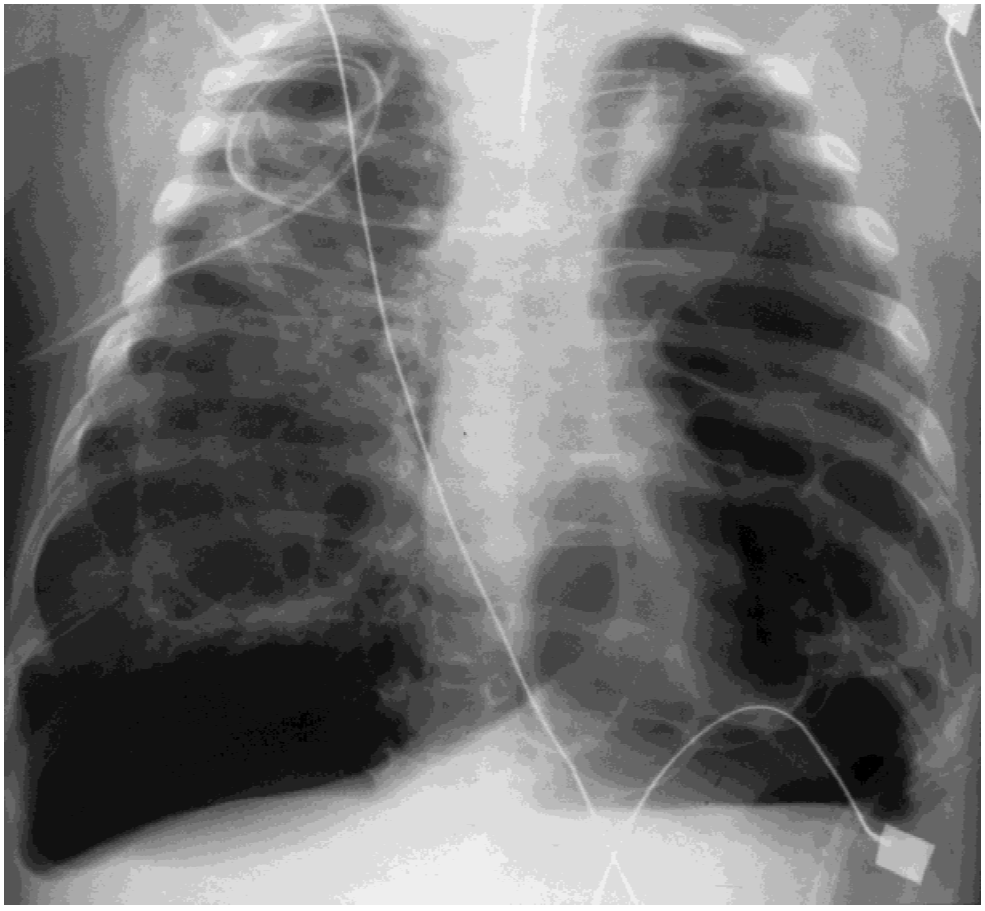

Fig. 2. Age 5 months. Chest radiograph shows bilateral pneumothorax treated with two pleural drains on the right side and one on the left side.

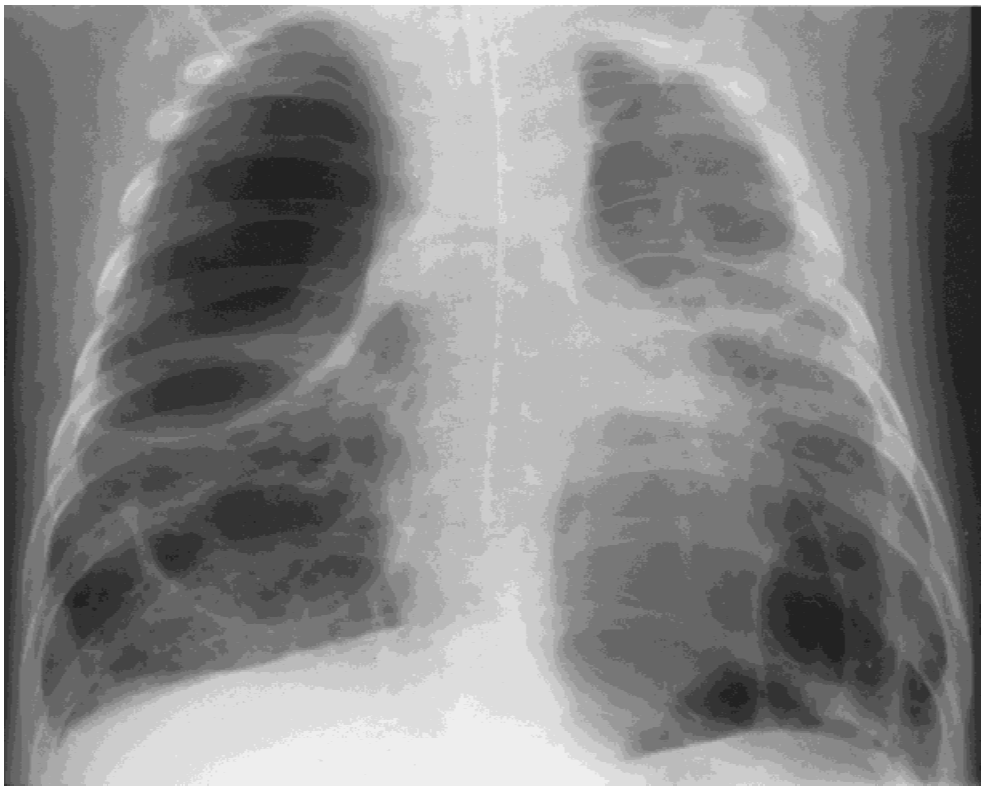

Fig. 3. Age 6½ months. Chest radiograph shows extensive bullae in both lungs.

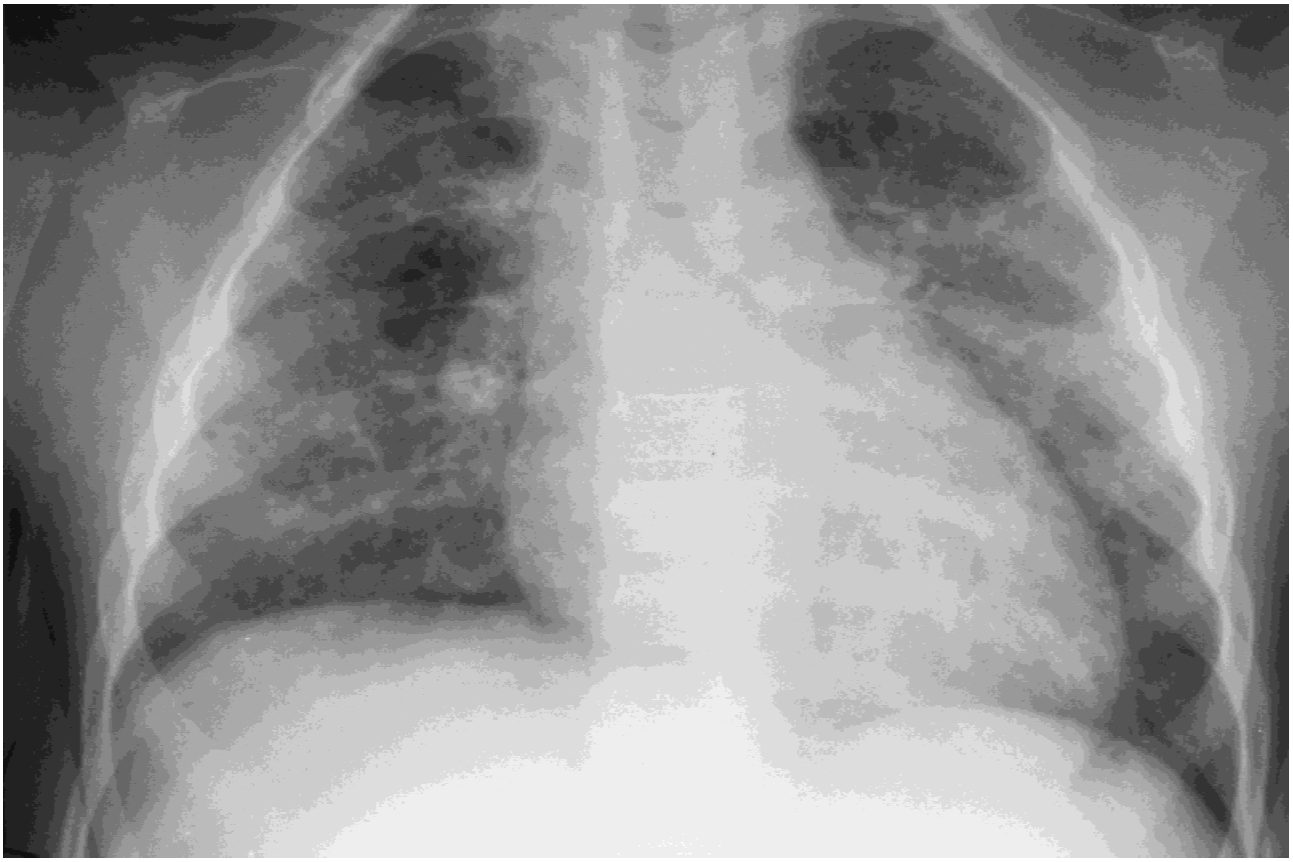

Fig. 4. Age 2 years, 8 months. Chest radiograph shows marked improvement with persistence of only a small bulla in the right lung.

duration ever reported in a child with LCH. The decision to go on with therapy for such a long time was based on the severity of the disease and her response to the drug. No serious side effects have been observed. CSA therapy did not prevent the development of diabetes insipidus. However, it is noteworthy that she suffered a local relapse (single bone lesion) a few months after reducing the intensity of CSA. Obviously, it is impossible to prove a correlation between dose reduction and relapse, but it was felt to be an important argument for continuing CSA therapy in an otherwise stable and uncomplicated situation.

Pulmonary involvement in multisystem LCH is reported in about 20–40% of cases [13,14]. In our patient, lung destruction due to large cysts and recurrent pneumothoraces was a prominent feature. In contrast to most reported patients, respiratory function was seriously reduced, and maximal respiratory support was required for several weeks. One important lesson from this case is that even severely damaged lung parenchyma seems to have a considerable capacity to recuperate. Obviously there must be normal lung tissue present, compressed between the cysts, and not readily appreciated on imaging studies.

We conclude that CSA was an effective rescue drug for our patient. Treatment of apparently extremely damaged lungs can be successful in LCH, leaving only moderate sequelae. Long-term treatment should be considered in case of multisystem LCH responding to CSA therapy.

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