A Case of Mediastinal T-cell Lymphoblastic Lymphoma Causing Superior Mediastinal Syndrome and Severe Complications

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ABSTRACT. A 3-year-old girl with T-cell mediastinal lymphoma causing superior mediastinal syndrome is described. The patient underwent biopsy under general anesthesia and received respiratory support thereafter. Intensive multi-agent chemotherapy was administered to cover malignancies other than malignant lymphoma and to overcome the life-threating complication. As a result, the patient developed tumor lysis syndrome in spite of prophylaxis. In addition, invasive fungal infection developed because of prolonged neutropenia. However, the patient recovered and achieved complete remission. When making treatment decisions for this condition, it is important to establish a diagnosis as soon as possible using a minimal degree of invasion.

Key words : non-Hodgkin's lymphoma — superior mediastinal syndrome — tumor lysis syndrome — invasive fungal infection

Superior vena cava syndrome due to a mediastinal mass can be caused by a variety of malignant tumors.[1] Occasionally, mediastinal tumors cause dyspnea by compressing the airway, and this is known as superior mediastinal syndrome.[2] This life-threatening complication requires an immediate treatment decision.

Malignant lymphoma is the third most common group of malignant solid tumors in children. Non-Hodgkin's lymphomas represent approximately 90% of those diagnosed, and comprise three histologic subtypes : small-noncleaved-cell, large-cell, and lymphoblastic lymphoma. Lyphoblastic lymphoma, especially of the T-cell phenotype, typically presents as a mediastinal mass. Of the 56 T-lymphoblastic lymphoma in a large series, 27 cases were showed mediastinal or pleural involvement.[3] In addition, lymphoblastic lymphoma is so highly chemotherapy-sensitive that treatment can cause tumor lysis syndrome.[4]

Here we report a juvenile case of mediastinal T-cell lymphoblastic lymphoma that caused respiratory distress and was treated under respiratory intervention. The patient also suffered from tumor lysis syndrome and invasive fungal infection.

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CASE REPORT

A 3-year-old girl was admitted to Kawasaki Medical School Hospital because of subcutaneous masses on the scalp and a mediastinal mass (Fig 1). The patient had been well until 30 days earlier, when her parents had noticed some nodules on the parietal scalp. Three weeks before admission, facial swelling had developed, and 10 days before admission a productive cough had appeared. She had been taken to a pediatric clinic where she had been prescribed antihistamine, and this had improved the facial edema and cough. However, the nodules on the scalp remained palpable, so the patient was seen by another dermatologist, and referred to our hospital for further examination.

The patient's temperature was 36.7°C, pulse rate was 96 beats/min, respiratory rate was 28 breaths/min and blood pressure was 102/58 mmHg. On physical examination, the patient appeared lethargic. Her face and neck were swollen, and some nodules were palpable on the parietal scalp. Several lymph nodes, 1-1.5 cm in diameter, were palpable in the bilateral neck. The oxygen saturation was 95% while the patient was breathing ambient air. Breath sounds were decreased in the right lung field. The heart appeared normal. The abdomen was soft and was neither distended nor tender. The liver and spleen were not palpable.

A chest X-ray examination showed a large mediastinal mass (Fig 2). Computed tomographic scan of the chest revealed a lobulated heterogeneous mass without calcification measuring 7 cm in the anterior mediastinum (Fig 3a). Pleural effusion was not evident. The hematocrit was 36.7%, the white cell count 20,400/mm^3, and the platelet count 130,000/mm^3. The serum levels of blood urea nitrogen, creatinine, and uric acid were 21 mg/dl, 0.31 mg/dl, and 9.7 mg/dl, respectively. The levels of glucose, bilirubin, total protein, albumin, globulin, aspartate aminotransferase, alanine

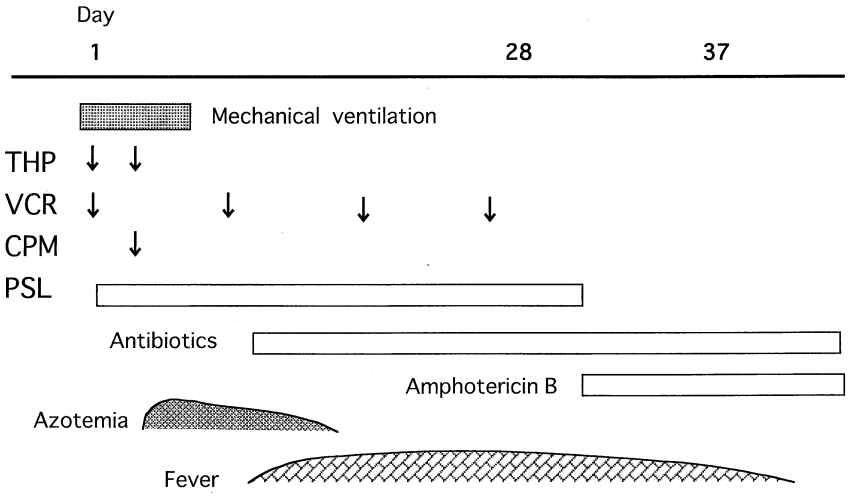

Fig 1. Clinical course
The patient underwent multiagent chemotherapy consisting of pirarubicin (THP), vincristine (VCR), cyclophosphamide (CPM), and prednisolone (PSL).

aminotransferase, alkaline phosphatase, sodium, potassium, chloride, phosphate, and calcium were normal.

The following day, some of the subcutaneous masses were enucleated under general anesthesia. Frozen sections of the biopsy specimens revealed small, round tumor cells. In the recovery room, sudden hypotension and cyanosis were observed, so the patient was re-intubated and deeply anesthetized with mechanical support. She was given 3000 ml/m^2 fluids with sodium bicarbonate intravenously, and allopurinol orally. She underwent chemotherapy including prednisolone, pirarubicin and vincristine, with hydration and alkalization. On the third hospital day, although the subcutaneous masses had become non-palpable, intravenous cyclophosphamide was additionally administered because of the lack of improvement in the patient's respiratory distress. The levels of BUN and creatinine became elevated to 34 mg/dl and 0.54 mg/dl respectively, despite the fact that urine

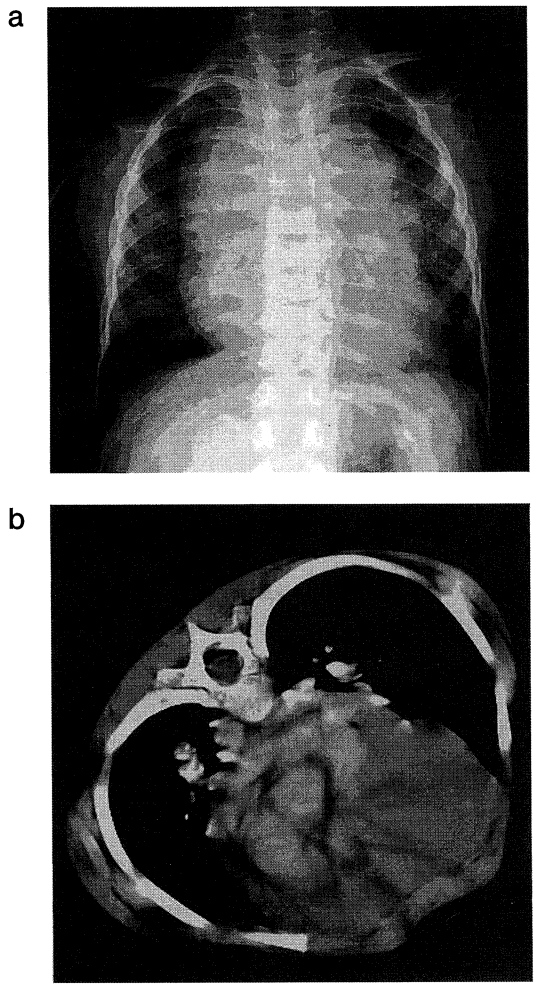

Fig 2. Chest radiograph (a) reveals the widened mediastinum. Computed tomography scan (b) demonstrates a homogeneous anterior mediastinal mass.

volume was maintained.

On the fourth hospital day, arterial oxygen partial pressure improved. Although the size of the mediastinal mass appeared to have reduced on a chest radiograph, a biopsy specimen revealed lymphoblastic lymphoma, so the protocol was cintinued. The azotemia resolved without dialysis, and the patient was weaned from mechanical ventilation on the sixth hospital day.

On the following day, her temperature rose to 39°C. Panipenem and aztrenam were administered intravenously. Fluconazole was also administered because the patient remained febrile for two days. On the 23rd hospital day, right parasternal pain developed. After intravenous substitution of ceftazidime, amikacin, amphotericin-B, and lenograstim for panipenem, aztrenam, and fluconazole, the fever subsided. Another chest CT scan on the 27th hospital day revealed that although the size of the mediastinum was within the normal range, a mass region surrounded by irregular ground-glass opacity was present in the right lung field. Serologic tests were positive for antibodies against *Aspergillus*. On the 29th hospital day oral itraconazole was substituted for amphotericin-B because of hypopotassemia and liver dysfunction. On the 37th hospital day, a bone marrow aspirate showed no evidence of the tumor, and complete remission was achieved. The antibiotics were withdrawn, and the patient received consolidation and

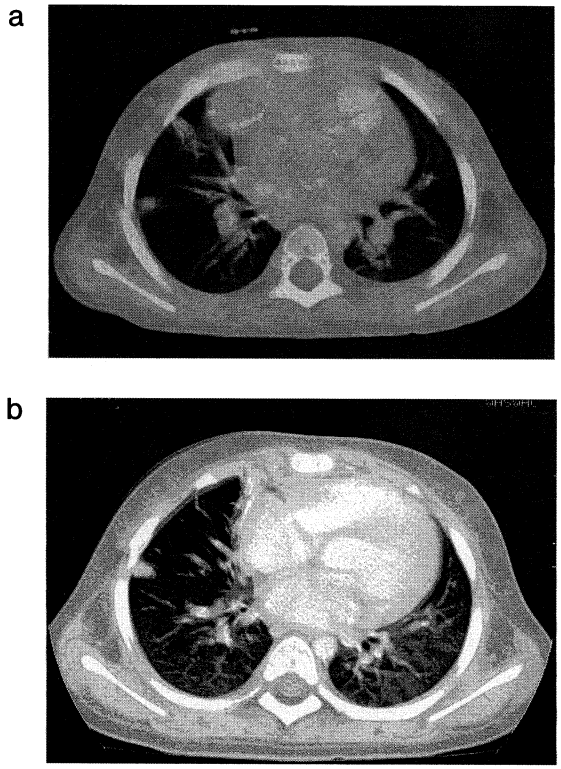

Fig 3. Computed tomography scan on the 27th hospital day (a) reveals a nodule with central lucency. Another computed tomography section on 50th hospital day (b) shows a scar.

maintenance chemotherapy. Another CT scan of the chest on the 46th hospital day showed a normal-size mediastinum and a small scar in the right lung field.

DISCUSSION

This juvenile patient had three severe complications: superior mediastinal syndrome, tumor lysis syndrome and invasive fungal infection.

Superior mediastinal syndrome (SMS) requires immediate treatment involving chemotherapy, radiation therapy, or both. We made a tentative diagnosis of malignant lymphoma based on chest CT findings and the histopathology of a frozen section of a biopsy specimen, and initiated therapy for malignant lymphoma with anthracycline and cyclophosphamide. However, a variety of malignant tumors in the mediastinum may cause SMS, and small round-cell tumors may include malignant tumors other than lymphoma, such as Ewing's sarcoma, neuroblastoma and rhabdomyosarcoma.[5] Half of 16 cases of superior vena cava syndrome raported at St Jude Children's Research Hospital were due to non-Hodgkin lyphoma.[1] To obtain specimens for pathological diagnosis, we undertook biopsy under general anesthesia. In terms of avoiding mechanical ventilation support, local anesthesia would have been more preferable. Narang *et al* described eight patients with mediastinal mass who suffered severe brain damage or death as a result of general anesthesia in Australia, the United Kingdom and the United States.[6] Bone marrow aspiration or cytology of a lumbar tap preceding biopsy might also aid a more rapid diagnosis.

Tumor lysis may occur in tumors like lymphoblastic lymphoma that are highly chemosensitive.[4] Prevention of tumor lysis syndrome entails hydration, alkalinization, and administration of allopurinol. Although our patient received all three treatment, azotemia developed after the introduction of intensive chemotherapy. When a diagnosis of malignant lymphoma has been made, low-dose chemotherapy such as prednisolone monotherapy should be given initially. Recently, an alternative agent, urate oxidase, has been introduced for management of hyperuricemia.[7]

The long-term survival of patients with advanced-stage lymphoblastic lymphoma has improved since the introduction of multi-agent chemotherapy based on protocols for the treatment of acute lymphoblastic leukemia.[8] Intensive chemotherapy often results in persistent neutropenia. Systemic fungal infections are therefore a major cause of morbidity and mortality in such immunocompromised patients.[9] In our patient, although fluconazole was administered in addition to antibiotics for neutropenic fever, new lesions appeared in the right lung field. A probable diagnosis of invasive aspergillosis was made on the basis of positivity for *Aspergillus* antigen.[10] Amphotericin B is effective for invasive aspergillosis, but fever, hypopotassemia and renal toxicity restrict its administration. Antifungal agents that are more effective, as well as less toxic, than amphotericin B, such as amphotericin B lipid complex and mikafungin,[11] will soon be available in Japan.

In conclusion, we have reported a case of mediastinal T-cell lymphoma causing respiratory failure. This life-threatening complication required immediate treatment, and we initiated intensive multi-agent chemotherapy to cover

malignancies other than malignant lymphoma. As a result, although the patient received prophylaxis, she developed tumor lysis syndrome. In cases such as the present one, physicians are advised to select the most effective therapy as soon as possible, and to pay attention to the possible development of tumor lysis syndrome.

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