

An Infant with Down Syndrome and Fever of Unknown Origin

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A 4-month-old boy with Down syndrome was admitted with fever for the past 2 months. The only additional complaint was respiratory distress when he was fed. He received amoxicillin, amoxicillin-clavulanate, ceftriaxone, and cefepime during four previous hospitalizations without improvement. He was transferred to our children's hospital to investigate fever of unknown origin. A Calmette-Guérin bacillus (BCG) vaccine was given at 50

days. His mother was HIV-negative, reported cough for more than 2 weeks, and close contact during pregnancy with a patient who died with contagious pulmonary tuberculosis. The mother's tuberculin skin test (PPD) was 10 mm. On admission, the patient's peripheral blood examination showed a white blood cell count of $7.7 \times 10^9/L$, with 64.2% neutrophils, 23.6% lymphocytes ($1.8 \times 10^9/L$ absolute count), 11.4% monocytes, 0.7% basophils, and 0.1% eosinophils.

Erythrocyte sedimentation rate was 5, and the C-reactive protein level was $< 6 \text{ mg/L}$. These tests were repeated four times, and the results were always similar to those reported above. PPD was negative. Chest X-ray showed increased heart size. Blood cultures were sterile, and echocardiogram showed congenital cardiopathy (patent foramen ovale and patent arterial channel) and pericardial effusion. As the patient presented a positive epidemiological history of possible exposure to

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For diagnosis, see page 194.

Editor's note: Each month, this department features a discussion of an unusual diagnosis in genetics, radiology, or dermatology. A description and images are presented, with the diagnosis and an explanation of how the diagnosis was determined following. As always, your comments are welcome; please e-mail pedann@slackinc.com.

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tuberculosis, isoniazid, rifampin, and pyrazinamide were given for 1.5 months under supervision.

Despite the therapy, he presented fever twice a day regularly. His respiratory distress worsened despite receiving digoxin, captopril, furosemide, and spironolactone. An alveolar pulmonary infiltrate was found on the chest X-ray. Ceftriaxone and vancomycin were then added, but the child died after the sudden worse of the respiratory distress. His mother completed a 6-month treatment with the same antituberculous drugs that were given to him, and full recovery was achieved.

PATHOLOGIC INVESTIGATION

At autopsy, patent foramen ovale, pericardial effusion, lung congestion, and tuberculous mediastinal lymphadenitis (acid-fast bacilli detected on Ziehl-Neelsen staining smear) were found. Hypoplasia of thymus (weight 3 g), spleen and lymph nodes was documented. In mediastinal lymph nodes, extensive necrosis and numerous bacillus were seen using Ziehl-Neelsen staining, and paracortical cells were markedly diminished (see Figure A-B). Absence of granulomas was observed. In the thymus, there was no clear definition between the cortex and the medulla, and lymphocytes were diminished (see Figure C-D). In the spleen,

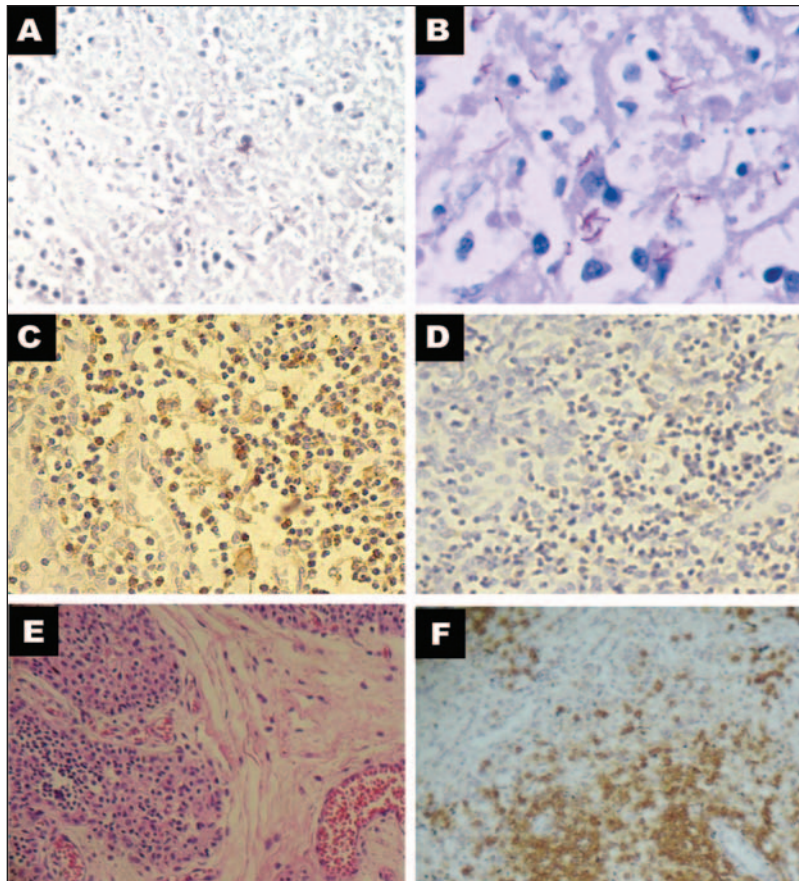


Figure. Histologic aspects of secondary lymphoid organs. (A-B) Ziehl-Neelsen staining of mediastinal lymph node 400X (A) and 1,000X (B), with extensive necrosis and numerous bacillus, paracortical cells markedly diminished, and absence of granulomas. (C) CD4 staining 400X and (D) CD8 staining 400X with a very low density in the thymus. (E) Spleen (H and E) 400X and (F) CD4 staining 400X in the spleen, with diminished lymphocytes around arterioles.

lymphocytes around arterioles were largely decreased (see Figure E-F). Immunohistochemistry by using the avidine-biotin-peroxidase method with specific antibodies anti-CD20 (B lymphocytes, data not shown), anti-CD4 (helper T lymphocytes), and anti-CD8

(cytotoxic T lymphocytes) revealed a very low density of helper and cytotoxic T lymphocytes in the thymus (see Figure C-D), in the spleen (see Figure F), and in the lymph nodes (not shown). No other organ was compromised by the mycobacterial infection.

DIAGNOSIS

Primary Mediastinal Tuberculosis

Patients with Down syndrome have increased frequency of infections, hematologic malignancies, and autoimmune diseases, such as celiac disease, hypothyroidism, and type 1 diabetes mellitus.¹ In a recent study, immunophenotyping of blood lymphocytes of 96 healthy children with Down syndrome showed that massive activation, proliferation, and maturation of T and B lymphocytes in response to environmental antigens was severely abrogated.² Such diminished expansion was attributable to a disturbance in the adaptive immune system, suggesting that immunodeficiency is an integral part of Down syndrome.² The underlying mechanism responsible for this finding remains unclear.²

According to current literature, fever of unknown origin is defined as documented fever of more than 7 to 10 days with no apparent source and no apparent diagnosis after 1 week of clinical investigation.³ Chronic infections, particularly tuberculosis, are of major concern in patients with fever of unknown origin because of their high frequency.³ Tuberculosis has been occasionally reported in patients with Down syndrome, and defects in the inflammatory response, cellular, and humoral immunity have been recognized.⁴

Because of the epidemiologic history (mother with chronic cough, recent exposure to a pa-

tient with pulmonary tuberculosis, and positive PPD) and the high frequency of tuberculosis among patients with fever of unknown origin, we started antituberculous treatment. His mother recovered after receiving the same treatment as he was given. Because the patient had primary tuberculosis that was probably acquired from his mother, resistance to the used

The underlying mechanism responsible for this finding remains unclear.

drugs was not of concern. Nonetheless, the patient died. White blood cells, C-reactive protein, and erythrocyte sedimentation rate were repeatedly normal despite the active mediastinal tuberculosis, implying low immune responsiveness to infection. The absolute number of peripheral lymphocytes was below the fifth percentile for his age ($3.7 \times 10^9/L$).⁵ At autopsy, severe compromising of the immune organs architecture was noted, suggesting a T cell immunodeficiency, and the histological aspects were similar to those described in patients coinfecting with tuberculosis and HIV.⁶ Thus, the immunodeficiency could have contributed to the treatment failure, despite the normal total leukocyte counts in the blood.

Despite doubling the median age of death to 50 years during the past 2 decades, mortality in Down syndrome remains higher than in the general population, and respiratory tract infections are ma-

ior causes.⁷ In a population-based study, children with Down syndrome had a significantly elevated risk of death from sepsis, with a mortality-rate ratio of 1.3 after adjusting for confounding factors, such as demographics, pathogens, and concomitant conditions.⁸ Thymic alterations have been described in Down syndrome: The overexpression of chromosome 21 encoded gene products leads to impaired interaction between immature thymocytes and thymic stromal cells.⁹ The histopathologic findings of the thymus of this case were in accordance with the reduction of thymocyte subpopulations described earlier in patients with Down syndrome.¹⁰ The complete sequencing of chromosome 21 may be the key to the understanding of the underlying pathogenic mechanisms of the immunological disturbances described in patients with Down syndrome.¹¹

CONCLUSION

This case highlights the necessity of performing immunologic evaluation in patients with Down syndrome who are difficult to treat. This fatal case of primary tuberculosis without lung involvement has not yet been presented in the literature. Special attention must be paid when patients with Down syndrome have mycobacterial infection.

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