

Case Report

Unusual and severe disease course in a child with ataxia-telangiectasia

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Ataxia-telangiectasia (AT) is an autosomal recessive syndrome of combined immunodeficiency. Hallmarks of the disease comprise progressive cerebellar ataxia, oculocutaneous telangiectasia, cancer susceptibility and variable humoral and cellular immunodeficiency. We describe a patient with AT presenting with autoimmune haemolytic anaemia, neutropenia, hepatosplenomegaly, lymphadenopathy and hyper-IgM at the age of 6 months. At the age of 26 months she developed persistent fever, progressive lymphadenopathy and pulmonary nodular infiltrates, which were responsive to steroid therapy.

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Ataxia-telangiectasia (AT) is a rare autosomal-recessive disorder characterized by cerebellar ataxia, ocular apraxia, cutaneous and conjunctival telangiectasia, immunodeficiency, defective cell cycle checkpoints and an increased risk of cancer, primarily lymphoid neoplasms. The defective gene in AT, ATM (AT mutated) resides on chromosome 11q22–23 and encodes a 370-kDa protein that belongs to a family of kinases (1). Over 400 mutations have been identified thus far. ATM seems to be involved in sensing double-strand breaks and has a role in cell cycle control (2, 3).

Severe immunodeficiency and infections are observed in approximately one-third of patients with AT, while another third have only mild immunodeficiency and the final third have little or no immunological problems and only seldom suffer from sinopulmonary infections (4). The immunodeficiency involves low or absent IgA

and IgG as well as a marked T lymphocytopenia. Typically, CD4CD45RA⁺ (naïve) T-cells are decreased (5, 6).

The diagnosis of AT is based primarily on the clinical findings. Elevated serum levels of alpha-foetoprotein are found in 98% of patients. Chromosome radiosensitivity is typically increased. Absence of ATM protein is diagnostic. Karyotyping may reveal characteristic translocations (2).

We describe a patient with AT and autoimmune haemolytic anaemia, neutropenia, hyper-IgM, hepatosplenomegaly, lymphadenopathy and pulmonary nodular infiltrates.

Case report

The patient was born term as the first child of healthy nonconsanguineous parents. She presented at the age of 4 months with fever of unknown

origin, received intravenous antibiotics and recovered. A haemogram showed mild thrombocytosis: haemoglobin 9.6 g/dl (age-corrected normal range 9.5–13.5 g/dl), white blood cell count $8.6 \times 10^9/l$ ($5.0\text{--}19.5 \times 10^9/l$), absolute neutrophil count $6.9 \times 10^9/l$ and platelet count $578 \times 10^9/l$ ($150\text{--}450 \times 10^9/l$). Cultures of blood, urine and cerebrospinal fluid remained sterile. No viruses were detected in stools or nasopharyngeal aspirate. At the age of 9 months, she was referred to our hospital with a diagnosis of otitis media and marked hepatosplenomegaly palpable up to 7 cm below the costal margin. Blood count revealed a normocytic anaemia, leukopenia and neutropenia: haemoglobin 8.1 g/dl (11.0–13.5/dl), mean corpuscular volume 82.1×10^{-12} ($75\text{--}86 \times 10^{-12}$), white blood cell count $3.6 \times 10^9/l$ ($6.0\text{--}17.5 \times 10^9/l$), absolute neutrophil count $1440 \times 10^9/l$ and platelet count $267 \times 10^9/l$ ($150\text{--}450 \times 10^9/l$). A decreased plasma haptoglobin level and a positive direct Coombs' test were suggestive of an autoimmune haemolytic anaemia. Anti-blood group A IgG and complement-mediated haemolysis were demonstrated. GOT and GPT but not γ GT were mildly elevated. Serology for HAV, HCV, HIV, Parvovirus B19, EBV, CMV, adenovirus and Toxoplasma all proved negative. Hepatitis B surface antigen antibodies after scheduled routine vaccination were present at a concentration of 23 IU/l in the absence of Hepatitis B surface antigen. Immunological evaluation revealed: IgG < 0.66 g/l (age-matched normal range 3.54–9.34 g/l), IgA 0.00 g/l (0.14–0.86 g/l), IgM 3.02 g/l (0.29–1.39 g/l), IgD < 38 U/ml (≤ 100 U/ml) and IgE < 2 kU/l (≤ 51 kU/l). Lymphocyte phenotyping revealed a total CD3 count of 1296 cells/ μ l (normal range 2300–5900 cells/ μ l) a decreased CD4 count of 1113 cells/ μ l (normal range 2400–5500 cells/ μ l), a decreased CD8 count of 207 cells/ μ l (normal range 500–2200 cells/ μ l), and a decreased CD19 count of 268 cells/ μ l (1300–2300 cells/ μ l). Lymphocyte proliferative response to mitogens and antigens were mildly decreased. HLA class I and II expression on lymphocytes was normal. Liver biopsy was performed and denoted aspecific changes. Ferritin was normal at 75 μ g/l (12–230 μ g/l).

The elevated IgM levels led to a presumptive diagnosis of hyper-IgM syndrome. CD40 ligand was present on T lymphocytes and CD40 was present on B lymphocytes at normal levels. An autosomal recessive form of hyper-IgM syndrome was thus suspected. Absence of IgE production by B-lymphocytes stimulated by IL-4, anti-CD40 or IL-4 + anti-CD40 were in

favour of this diagnosis (performed by A. Fisher, Hôpital Necker, Paris). Substitution therapy with monthly intravenous immunoglobulin and *Pneumocystis carinii* prophylaxis were initiated. Under this treatment severe infections were rare.

At the age of 23 months unsteady gait was noted on physical examination. A diagnosis of AT was suspected. Alpha-fetoprotein at this stage was 93.5 ng/ml (normal range < 12.5 ng/ml). Further investigation revealed a decreased subpopulation of CD4 CD45RA⁺ cells (naïve T-cells). Cytogenetic studies on peripheral blood cells showed a translocation t(7;14) and inv(7). However, radiosensitivity of the lymphocytes demonstrated only a slight increase in chromosomal breakage after radiation with 1 Gy compared to controls. ATM protein analysis by Western blotting with monoclonal antibody to a 3'-peptide of ATM demonstrated absence of the protein thus confirming the diagnosis of AT. ATM gene analysis for the common mutations is in process.

At the age of 26 months, the patient presented with a prolonged episode of fever. She had a mild cough. On physical examination the hepatosplenomegaly was still present and cervical and submandibular lymphadenopathies were found. IgM was markedly elevated up to 9.14 g/l and IgG trough levels dropped to 3.85 g/l despite continuous monthly substitution with 700 mg IgG/kg. Computed tomography revealed several enlarged cervical lymph nodes, mediastinal lymphadenopathy as well as diffuse pulmonary nodular interstitial infiltrates. A lymph node biopsy showed numerous IgM-laden histiocytes corresponding to pseudo-pseudo-Gaucher cells. There was no evidence of malignant proliferation. Bone marrow biopsy revealed no abnormalities. In view of the abnormalities on chest imaging, a bronchoalveolar lavage was performed. No infectious aetiology or aberrant cytology could be found. A tentative diagnosis of lymphocytic interstitial pneumonia (LIP) was made and prednisolon 2 mg/kg/day was initiated. Response was prompt: the fever disappeared, mediastinal and cervical lymphadenopathy decreased and IgM levels dropped. Therapy was continued for a further 4 months on an alternate-day base before tapering completely. Two months later, lymphadenopathy recurred, together with subfebrillitas. Steroid therapy was reinitiated. Throughout the clinical course lymphocytopenia ($200\text{--}1000 \times 10^9/l$) and neutropenia ($1000\text{--}1500 \times 10^9/l$) persisted.

Discussion

This child presented with autoimmune haemolytic anaemia, neutropenia, and hepatosplenomegaly,

absent IgA and IgG and hyper-IgM. At first, although rare, an autosomal recessive hyper-IgM syndrome was suspected. However, as the clinical picture evolved, the diagnosis of AT was made.

The frequent association between autoimmune haemolytic anaemia and AT and other immunodeficiency syndromes has been addressed. However, a pathophysiological link with ATM has not been established.

Hyper-IgM occurs in 1–2% of patients with AT and is believed to be the result of a polyclonal rather than of a monoclonal proliferation. Occasional patients have been described with very high IgM levels, splenomegaly, lymphadenopathy and neutropenia (2). Recently, Tangsinmankong et al. described a similar case of an AT patient presenting with lymphocytic interstitial pneumonitis (LIP), hepatosplenomegaly and hyper-IgM. Indeed, both their and our patient proved to have high IgM in absence of IgG and IgA. Moreover, both had very low CD8 counts (43 and 207 cells/ μ l, respectively) with a high CD4/CD8 ratio (9 and 5, respectively) in contrast to the low CD4/CD8 ratio usually found in AT. Tangsinmankong et al. suggested that hyper-IgM in subjects with AT may represent an inefficient immunological response to infection (7). We speculate that hyper-IgM and relatively decreased CD8 counts delineate the clinical entity of lymphadenopathy, hepatosplenomegaly and LIP in AT. The generalized lymphadenopathy and the hepatosplenomegaly might well fit in a myeloma-like gammopathy that is sometimes associated with hyper-IgM in AT and that can be associated with signs of hyperviscosity (2). The demonstration of pseudo-pseudo-Gaucher cells supports this statement (8). There is some evidence that up-regulation of CD40 ligand gene underlies these findings (9).

The association between LIP and immune deficiency in general and abnormalities in immunoglobulin production, auto-immunity and HIV infection in particular has been described (5, 10, 11). The findings on lung scanning, the absence of neoplastic changes on lymph node biopsy, the absence of infectious agents on bronchoalveolar lavage and (in retrospect) the prompt response to treatment with steroids, were in favour of the diagnosis of LIP. Some cases of LIP respond well to treatment with steroids both clinically and radiologically (12, 13).

LIP, hepatosplenomegaly and generalized lymphadenopathy are likely to form part of a histopathological spectrum of lymphoid lesions, ranging from nonspecific lymphoid hyperplasia to atypical lymphoid hyperplasia and true lymphoid neoplasia. It is known that AT is the

genetically determined immunodeficiency syndrome with the greatest risk of lymphoma development (10% of patients) (2).

Conclusion

Ataxia-telangiectasia is a rare syndrome characterized by cerebellar ataxia, oculocutaneous telangiectasia, cancer susceptibility and combined immunodeficiency. We present a patient with AT and an unusual extended syndrome of hyper-IgM, lymphadenopathy, hepatosplenomegaly and pulmonary nodular infiltrates. We suggest that each patient presenting with an unexplained immunodeficiency syndrome with decreased immunoglobulin levels in the presence of B cells and with decreased CD4 cell number has plasma AFP levels and radiosensitivity of lymphocytes tested.

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