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Ataxia Telangiectasia Complicated by A Malignant Tumor of The Orbit

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Introduction

Ataxia telangiectasia is an autosomal recessive inherited disease caused by a mutation in the ATM gene mapped to *11q22-23*, encoding a large protein involved in cell cycle regulation and cytoprotection 1. Diagnosis is usually easy based on the association of a clinical triad: neurological signs, telangiectasias, increased susceptibility to infections and an increased risk of cancers.

Its incidence is estimated at 1 case /300,000 births. It is more important in populations with a high rate of consanguinity since it is an autosomal recessive disease caused by the mutation of the ATM gene. This genetic anomaly is also responsible for DNA repair problems exposing a susceptibility to develop malignancies.

Observation

Adam, 9 years old, followed for an ataxia-telangiectasia since the age of 7 years revealed by balance disorders at the age of 5 years, associated with telengoectasias and recurrent respiratory infections. The child was put on antibiotic prophylaxis and monthly immunoglobulin infusions. He was admitted with a picture of orbital cellulitis consisting of a left palpebral edema and ptosis associated with bilateral cervical adenopathies that had been evolving for one month prior to his admission, in a context of fever of 39°C and preservation of the general condition.

Clinical examination on admission found a conscious patient, pale le, febrile at 39°C, hemodynamically and respiratorily stable and hypotrophic at 19kg (-3DS).

The ophthalmological examination showed a periorbital swelling of the left eye, red and painful to palpation, with complete palpebral closure, lacrimation and left ptosis.

Figure 1: Left orbital cellulitis associated with right ptosis.

The neurological examination revealed a cerebellar ataxia made of balance disorders, a shaky walk with enlargement of the sustentation polygon and a dysarthria. Examination of the lymph nodes revealed bilateral jugular and occipital polyadenopathies of 2 cm in size, mobile in relation to the superficial plane and fixed in relation to the deep plane, with no inflammatory signs. The rest of the examination did not reveal any abnormalities apart from bilateral perlachia.

The biological work-up showed a CRP of 90.5 mg/l and a PCT of 0.16 ug/l, the haemogram showed an anaemia of 8g/dl

microcytic hypochromia, a leuco-neutropenia of 1210 elements/mm3 and a lymphopenia of 780 elements/mm3.

Cranio-orbital CT showed an appearance related to a collected left pre-septal orbital cellulitis complicating ethmoidomaxillary sinusitis.

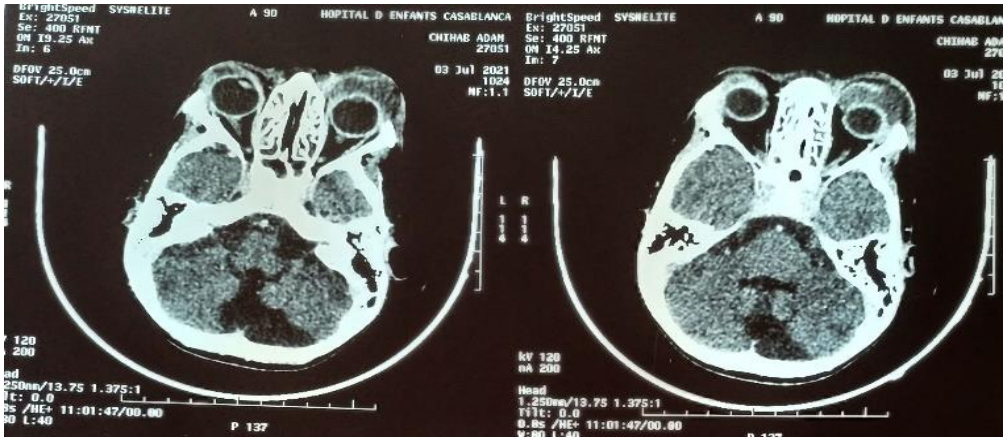

Figure 2: Left pre-septal orbital cellulitis collected Chandler IV.

In light of the clinico-biological elements a bacterial orbital cellulitis was retained. The patient was put on ceftriaxone 100mg/kg/d IV, metronidazole 30mg/kg/d IV and amikacin 15mg/kg/d IV for 10 days.

As there was no improvement after 10 days of treatment, another cranio-orbital scan was performed which showed persistence of septal and pre-septal orbital cellulitis extending over 18 mm, filling of the ethmoidal cells and thickening in a frame, with partial filling of the maxillary sinuses

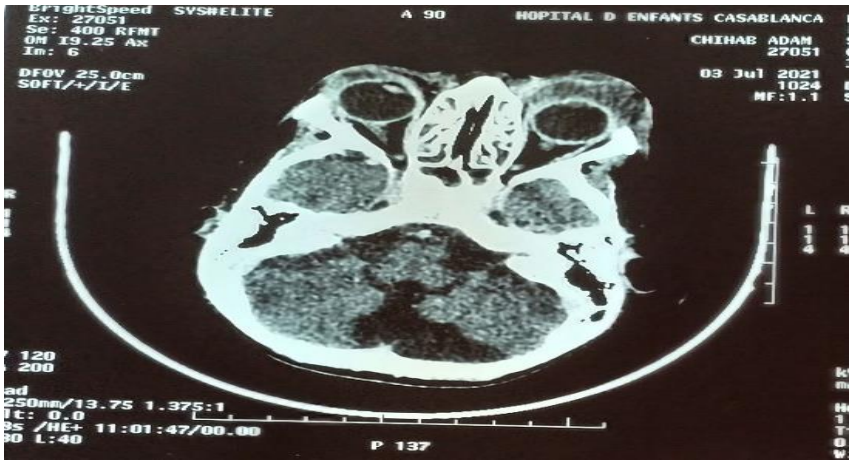

Figure 3: Ethmoidal cell filling and frame thickening and partial filling of the maxillary and sphenoidal sinuses.

This required a surgical exploration which revealed a purulent collection with suspicion of a fleshy tissue formation at the internal level. A biopsy was performed and the histopathological examination showed a malignant tumor proliferation with largely necrotic round cells. The immunohistochemistry study showed a malignant tumor proliferation with undifferentiated round cells, expressing CD4. The evolution was marked by the death of the patient in a picture of severe respiratory distress.

Discussion

Ataxia-telangiectasia associates a mixed immune deficiency mainly concerning humoral immunity due to the inactivation by mutation of the *ATM* gene (11q22.3) [10, 11]. The phenotypic expressions of this gene are multisystemic, which testifies to the multitude of functions of the ATM protein which is expressed differently depending on the target organ [12]. This gene, whose expression is ubiquitous, codes for a protein kinase playing a key role in the control of DNA double-strand break (DSB) repair, notably in cerebellar Purkinje cells and in endothelial cells (cerebral, cutaneous and conjunctival) [13]. ATM is involved in the detection of DNA damage and helps control the rate of growth and cell division. Also noteworthy is the frequency of acquired chromosomal aberrations affecting genes encoding the immunoglobulin superfamily relevant to immunoglobulin or T-receptor synthesis (7p14, 7q35, 14q12, 14q32) [11,12]. These acquired chromosomal abnormalities are at the origin of neoplasia. They are related to the defect in the function of the ATM protein in its role of DNA damage vigilance and cell cycle regulation [4]. An increased serum level of alpha-fetoprotein remains a strong argument for the diagnosis of AT. There seems to be a phenotype-genotype correlation: truncating mutations are responsible for the most severe

and early onset of the disease, whereas mutations that allow transcription of the protein lead to less severe disease. A residual activity of 50% of the ATM protein, as in heterozygotes, preserves the disease [1].

Ataxia-telangiectasia is an inherited multisystemic syndrome of chromosomal instability. The significant increase in cancer risk is a major clinical challenge, particularly in early childhood and adolescence. The high incidence of hematologic malignancies raises the question of whether correction of the hematopoietic system would prevent malignancies. There is evidence that cancer incidence correlates with ATM mutations that have resulted in a complete loss of gene product expression or function [15].

The predisposition to cancer in TA is significant and is the second leading cause of death after infections. The average age of onset of cancer of any type is 14 years (7).

The severity of neurological, immune and pulmonary damage varies greatly from one individual to another. Ataxia is the first symptom to appear, generally at the time of learning to walk 5. Progression of neurological symptoms leads to severe disability. Speech impediments appear, as well as choreoathetoid movements, while nystagmus develops and muscle weakness usually progresses to amyotrophy.

Telangiectasias may not appear until 4 to 6 years of age ; they predominate mostly in the conjunctiva of the eye, ears, elbow creases, popliteal fossae, and neck [14]

Lymphoid malignancies are the most frequent, 60% of which are non-Hodgkin's lymphomas of T phenotype. Acute lymphoblastic leukemias (ALL): constitute 23% of these hemopathies with cytogenetic characteristics identical to those of ALL of normal children (89,90). Whereas, T prolymphocytic leukemia, very rare in normal children, is much more frequent in AT homozygotes.

The magnitude of cancer risk for carriers depends on age, sex, and cancer type. AT heterozygotes appear to be predisposed to early cancer onset as are AT patients, but reports of gender distribution are inconsistent. Swift et al. [16].

Therapeutically, there is currently no curative treatment for ataxia-telangiectasia . Nevertheless, there are symptomatic treatments for the various manifestations of the disease.

Infections are treated with antibiotic therapy Antibiotic prophylaxis and regular infusion of immunoglobulins may be indicated in some cases to reduce the number of infections. Some therapeutic solutions by drugs are also under development: antioxidant that allow in some types of mutations to obtain a normal ATM protein 6.
In cases of malignancy, radiation therapy and some chemotherapies should be used with caution because of the sensitivity to X-rays of cells in patients with AT 9.

The prognosis remains guarded and is dominated by respiratory infections, neurodegenerative syndrome, accelerated mucocutaneous aging and high risk of cancer.

Conclusion

Ataxia telangiectasia is a rare condition with multisystemic expression, neurological, oculocutaneous and sinopulmonary, testifying to the complex and variable role of the ATM protein. The prognosis is severe, particularly related to the risk of infections and malignant degeneration.

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