Ataxia-Telangiectasia: Atypical Presentation and Toxicity of Cancer Treatment

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ABSTRACT: *Background:* The onset of progressive cerebellar ataxia in early childhood is considered a key feature of ataxia-telangiectasia (A-T), accompanied by ocular apraxia, telangiectasias, immunodeficiency, cancer susceptibility and hypersensitivity to ionizing radiation. *Methods:* We describe the clinical features and course of three Mennonite children who were diagnosed with A-T following the completion of therapy for lymphoid malignancies. *Results:* Prior to cancer therapy, all had non-progressive atypical neurological abnormalities, with onset by age 30 months, including dysarthria, dyskinesia, hypotonia and/or dystonia, without telangiectasias. Cerebellar ataxia was noted in only one of the children and was mild until his death at age eight years. None had severe infections. All three children were "cured" of their lymphoid malignancies, but experienced severe adverse effects from the treatments administered. The two children who received cranial irradiation developed supratentorial primitive neuroectodermal tumors of the brain, an association not previously described, with fatal outcomes. *Conclusions:* The range of neurological presentations of A-T is broad. Ataxia and telangiectasias may be minimal or absent and the course seemingly non-progressive. The diagnosis of A-T should be considered in all children with neuromotor dysfunction or peripheral neuropathy, particularly those who develop lymphoid malignancies. The consequences of missing the diagnosis may be dire. Radiation therapy and radiomimetic drugs should be avoided in individuals with A-T.

RÉSUMÉ: Mode de présentation atypique et toxicité du traitement anticancéreux chez les patients atteints d'ataxie-télangiectasie. *Contexte :* L'apparition d'une ataxie cérébelleuse progressive dans la petite enfance est considérée comme une manifestation clé de l'ataxie-télangiectasie (A-T), accompagnée d'apraxie oculaire, de télangiectasies, d'un déficit immunitaire, de susceptibilité au cancer et d'hypersensibilité aux radiations ionisantes. *Méthodes :* Nous décrivons les manifestations cliniques et l'évolution chez trois enfants mennonites chez qui un diagnostic d'A-T a été posé après un traitement pour cancer lymphoïde. *Résultats :* Avant le traitement anticancéreux, tous présentaient des anomalies neurologiques atypiques non évolutives, dont l'âge de début se situait vers 30 mois, soit de la dysarthrie, des dyskinésies, de l'hypotonie et/ou de la dystonie sans télangiectasies. Une ataxie cérébelleuse a été notée chez un seul des enfants et elle est demeurée légère jusqu'à son décès à l'âge de huit ans. Aucun n'a présenté d'infection grave. Les trois enfants ont été « guéris » de leur cancer lymphoïde. Cependant tous ont présenté des effets secondaires du traitement. Les deux enfants qui ont reçu une irradiation crânienne ont présenté des tumeurs cérébrales neuroectodermiques primitives sus-tentorielles, une association jamais décrite auparavant, dont l'issue a été fatale. *Conclusions :* Le mode de présentations neurologiques de l'A-T est vaste. L'ataxie et les télangiectasies peuvent être minimes ou absentes et sans évolution apparente. Le diagnostic d'A-T devrait être envisagé chez tous les enfants qui présentent une dysfonction neuromotrice ou une neuropathie périphérique, surtout chez ceux qui présentent éventuellement un cancer lymphoïde. Si le diagnostic n'est pas posé, les conséquences peuvent être sérieuses. La radiothérapie et les médicaments radiomimétiques devraient être évités chez les individus atteints d'A-T.

Ataxia-telangiectasia (A-T) is an autosomal recessive genomic instability syndrome characterized by progressive cerebellar ataxia, oculocutaneous telangiectasias, immunodeficiency, hypersensitivity to ionizing radiation, and cancer predisposition, with lymphoid malignancies predominating in the first two decades of life[1-10]. Mutations in the Ataxia-telangiectasia mutated (ATM) gene result in markedly decreased or absent levels of ATM kinase, a protein that phosphorylates many downstream targets. A deficiency of ATM kinase leads to cell cycle defects, faulty repair of DNA damage, defective apoptosis, and poor responses to oxidative stress[1,3,11].

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We describe three Mennonite children who were diagnosed with A-T after completing treatment for lymphoid malignancies. All had mild, atypical, seemingly non-progressive pre-existing neurological abnormalities, without telangiectasias. Subsequently, all suffered severe adverse effects of cancer therapy; two developed supratentorial primitive neuroectodermal tumors (PNET) of the brain following cranial irradiation.

CASE REPORTS

Patient 1 (Index case)

This child was born at term to a Mennonite mother and a Salvadorian father. Consanguinity was denied. The family history was positive for dystonia in several maternal male and female cousins, many of whom are now over 30 years old; none were available for examination. The child was noted to be clumsy at age one year, when he began to walk. Speech was delayed. He was diagnosed with T-cell acute lymphoblastic leukemia (T-ALL) without central nervous system involvement at age 20 months. He was treated with multiagent systemic chemotherapy, intrathecal chemotherapy, cranial irradiation (1800 centiGray [cGy]) and mediastinal irradiation (300 cGy), according to Pediatric Oncology Group Protocol 9404. He did not experience excessive toxicity during treatment. His care was transferred to our center three months after he completed therapy. Dysarthria, jerky movements of the eyes, face, head and neck, generalized dyskinesia, and mild ataxia were noted at that time, with no telengiectasias. He drooled continually. His mother did not feel that his neurological function had deteriorated since infancy.

A serum alpha-fetoprotein (AFP) level was performed as a screening test for A-T when he was four years and four months old, and was elevated (Table). Subsequent testing confirmed the diagnosis of A-T (Table and Figure 1). Magnetic resonance imaging (MRI) of the brain was normal, as were his serum IgG, IgA, and IgM levels.

At age seven years and nine months, he presented with recurrent vomiting and lethargy. Magnetic resonance imaging of

Table: Results of testing for Ataxia-Telangiectasia (A-T)

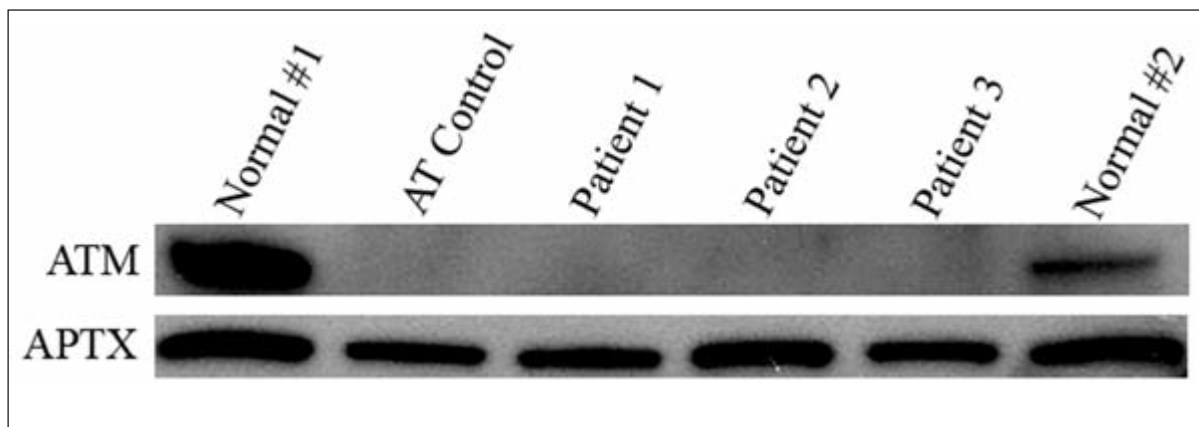| Patient	1	2	3
Age at diagnosis of A-T	4 y, 4 mo	10 y	17 y
Serum AFP* (µg/L)	135	32	178
Rearrangements of chromosomes 7 & 14†	Increased	Increased	Increased
Colony Survival Assay (Survival fraction)‡	19%	20%	6%
ATM Protein§	Absent	Absent	Absent

*Serum Alpha-fetoprotein: Normal range 0-7 after age two years; †Cytogenetic analysis of spontaneous and bleomycin-treated peripheral blood lymphocytes[57]; ‡Radiosensitivity assay. Diagnostic range is <21%[60,61]; §Ataxia-telangiectasia mutated protein (immunoblot)[35].

the brain showed two mixed cystic and solid tumors with peripheral enhancement, including one in the left temporoparietal region (5.2 to 5.8 cm diameter) and one in the left occipital lobe (2.5-3.1 cm diameter) (Figure 2). The histologic diagnosis was supratentorial PNET (Figure 3). Gross residual tumor remained following surgery. The family opted for palliation. The child died four months later. An autopsy was not performed.

Patient 2

This child was born at term to Mennonite parents, who were second cousins. The family history was positive for familial dystonia in several paternal male and female relatives, including the father's sister, who is now over 50 years old and has cervical dystonia. The child was noted to have poor balance and coordination when he started to walk at age one year. He

Figure 1: *Immunoblot of nuclear lysates, developed with antibodies to ATM and Aprataxin (APTX) (loading control). Note absence of ATM protein in Patients 1, 2 and 3.*
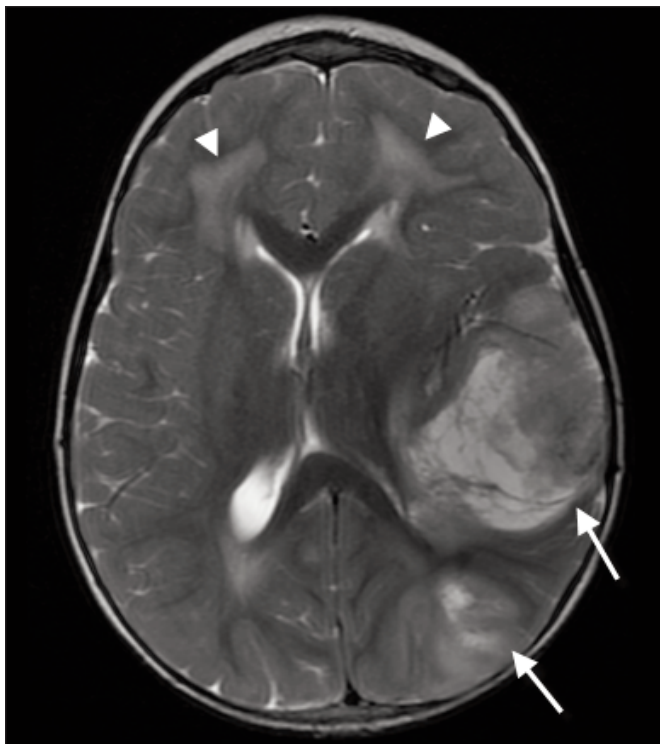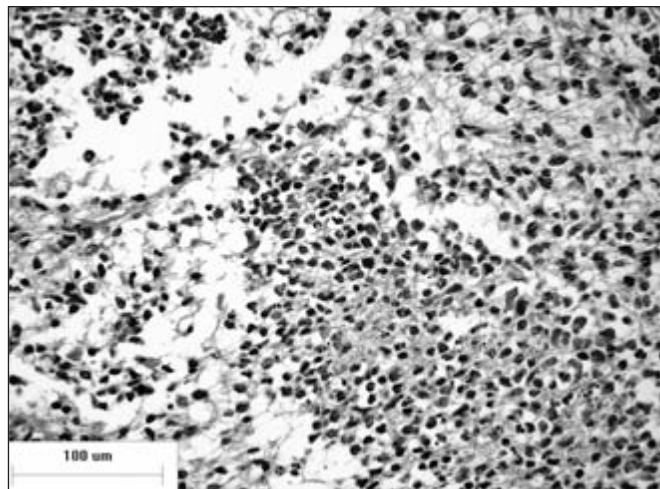
Figure 2: Patient 1: Axial T2-weighted MRI at level of basal ganglia showing multifocal PNET (arrows) and white matter injury from previous chemotherapy and radiotherapy (arrowheads).

Figure 3: Patient 1: Microscopic examination of the tumor showed a highly cellular small cell neoplasm with brisk mitotic activity and necrosis. The cells were immunoreactive for S100, neuron specific enolase (NSE), synaptophysin, protein gene product 9.5 (Pgp9.5), neuronal nuclei (NeuN) (regional), Ki67 (>50%) and glial fibrillary acidic protein (GFAP) (very rare), but not epithelial membrane antigen (EMA) or cytokeratin CAM5.2. The final diagnosis was supratentorial PNET (WHO grade IV).

exhibited choreiform posturing of his hands and twisting movements of his mouth. He was diagnosed with familial dystonia. He did not have telangiectasias, then or subsequently. His development was normal.

He was diagnosed with high-risk T-cell ALL with central nervous system involvement at age 31 months. Computed tomogram scan of the brain performed with and without contrast revealed no significant abnormalities. He received multiagent chemotherapy, intrathecal methotrexate, and craniospinal irradiation (2400 cGy to the brain and 600 cGy to the spine), according to regimen C of Children's Cancer Group protocol 1882. He exhibited neurodevelopmental regression ten months after starting therapy, and was considered to have severe treatment-related leuko-encephalopathy, a diagnosis supported by MRI of the brain. He completed therapy at age six years. Seizures, growth hormone deficiency, hypothyroidism, precocious puberty, bilateral conductive hearing loss, and scoliosis were diagnosed between ages eight and ten years.

Because of the severe adverse effects that he experienced from radiation therapy, his pre-existing neurological abnormalities, and our experience with the index case, he was evaluated for A-T at age ten years. His serum AFP level was elevated (Table). Subsequent testing confirmed the diagnosis of A-T (Table and Figure 1).

The child developed a right hemiparesis and lethargy at age 12 years. An MRI of the brain showed two mixed solid and cystic tumors, including one in the left parieto-occipital lobe (4.3 to 6.2 cm in diameter), and one in the left parietal region (1.7 to 2.8 cm diameter) (Figure 4). The solid portion of the masses showed avid gadolinium enhancement. The histologic diagnosis was supratentorial PNET (Figure 5). Gross residual tumor remained following surgery. The family opted for palliation. The child died six months later. An autopsy was not performed.

Patient 3

This child was born at term to an Australian mother and a Mennonite father. Patients 2 and 3 were second cousins. Patient 3 was not related to Patient 1 by family history. Generalized hypotonia was evident by age 30 months, accompanied by delayed fine motor skills, clumsiness, and slurred speech. His handwriting was subsequently noted to be slow and disorganized. At age 12 years he presented with generalized lymphadenopathy and was diagnosed with stage IV T-cell lymphoblastic non-Hodgkin lymphoma, with bone marrow involvement, but no central nervous system involvement. He was lymphopenic, with an absolute lymphocyte count of 0.675×10^9/L (normal 1.2 to 5.2). Serum IgG, IgA, and IgM levels were normal. He received intensive multiagent chemotherapy and intrathecal methotrexate, without radiation therapy, according to Children's Cancer Group protocol 5941. He completed treatment at age thirteen years and six months. He had significant problems with peripheral neuropathy, a toxicity which was likely due to vincristine, and which has still not completely resolved.

Because of his pre-existing neurological abnormalities and his relationship to Patient 2, he was screened for A-T at age seventeen years. His serum AFP level was elevated (Table).
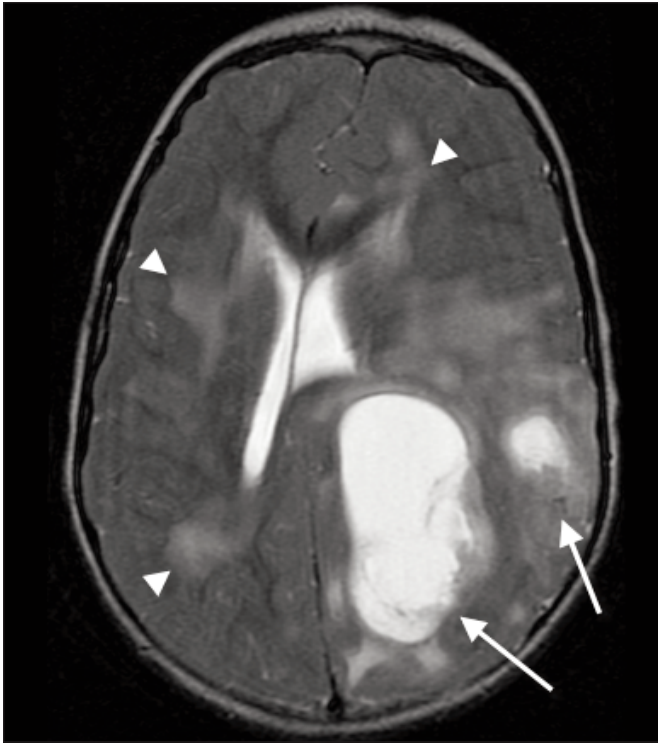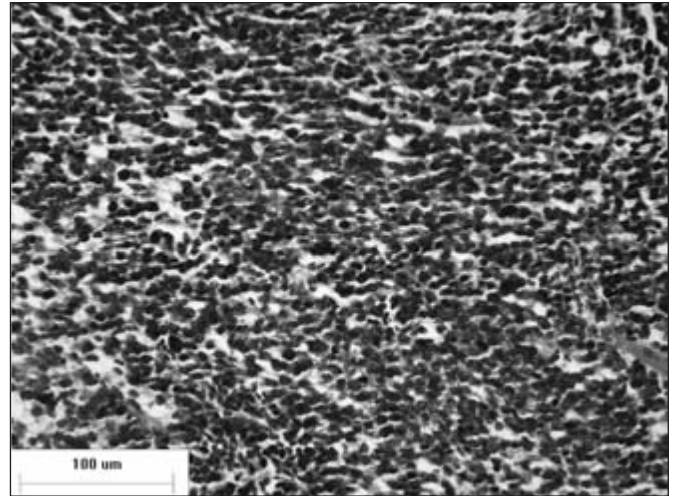
Figure 4: *Patient 2: Axial T2-weighted MRI at level of lateral ventricles showing multifocal PNET (arrows) and white matter injury from previous chemotherapy and radiotherapy (arrowheads).*

Figure 5: *Patient 2: Microscopic examination of the tumor showed a highly cellular small cell neoplasm with brisk mitotic activity and endothelial hyperplasia. The cells were immunoreactive for Pgp9.5, synaptophysin (regional), NeuN (rare), and Ki67 (~20%), but not GFAP or cytokeratin CAM5.2. The final diagnosis was supratentorial PNET (WHO grade IV).*

Subsequent testing confirmed the diagnosis of A-T (Table and Figure 1). At age 23 years, his neurologic status is stable. He remains cancer-free.

DISCUSSION

Individuals with "classic" A-T are usually ataxic by age two years, and are often wheelchair-bound by age ten years. Telangiectasias are typically evident by age six to ten years[1,11-13]. Our patients had seemingly non-progressive neurological abnormalities, including dysarthria, dyskinesia, generalized hypotonia and/or dystonia, and drooling, without telangiectasias. Only Patient 1 was ataxic when first referred. None had excessive problems with recurrent infection, even while receiving treatment for their lymphoid malignancies.

Milder phenotypes or atypical presentations of A-T have been described in the literature[1,11,13-28]. Some individuals with A-T have no neurological signs or symptoms[17]. Others have no telangiectasias, even in adulthood[1,11,13]. Mild ataxia, the onset of ataxia in adulthood,[21,23] slow neurological deterioration[20], a progressive axonal sensorimotor polyneuropathy[29-32], and late-onset spinal muscular atrophy[25] have also been described. Extrapyramidal features are more prominent in older children. Dystonia[22,28] or chorea[26] may be the initial or most prominent manifestation of A-T. Oculomotor apraxia[33,34], drooling, progressive hypomimia, slow speech with abnormalities of articulation, and progressive difficulty with chewing and swallowing are commonly seen[2,4-6,12,23]. Handwriting is typically affected by age eight years[11].

Milder A-T phenotypes are sometimes associated with missense mutations and/or reduced (but detectable) amounts of ATM protein[1,14,19-21,24,27,35]. Our A-T patients had a "milder" neurological phenotype. However, they had no ATM protein and did not have missense mutations, nor did they have the c.5932 G>T ATM mutation previously reported in other Mennonite families[36,37]. The results of their genotyping and haplotyping analyses are beyond the scope of this paper and will be reported subsequently.

The lifetime frequency of cancer in A-T patients approaches 38%[9], with 5% of patients developing more than one malignancy[3]. As exemplified by our patients, the diagnosis of malignancy may precede the diagnosis of A-T[38,39]; management of the cancer may be confounded by increased sensitivity to ionizing radiation and radiomimetic drugs[39-45].

Patients 1, 2, and 3 were cured of their lymphoid malignancies. However, all had severe adverse effects from the treatment that they received. Patient 3 had a severe peripheral neuropathy which was likely due to vincristine. This is in keeping with the reported heightened sensitivity to the neurotoxic effects of vincristine seen in individuals with neuromuscular disorders[43].

Patients 1 and 2 received cranial irradiation; both developed a second malignant neoplasm (a supratentorial PNET of the brain). This was likely radiation-induced, and had a fatal outcome. While medulloblastomas[41,46,47], astrocytomas[9,46,48-51], craniopharyngiomas[52], and primary central nervous system (CNS) lymphomas[53] have been described in individuals with A-T, supratentorial PNET's have not. Also of note is that ATM gene mutations do not appear to play a role in the pathogenesis of

medulloblastoma in children who do not have A-T[54]. The development of a PNET of the brain following cranial irradiation has been described in individuals without A-T, but is very uncommon; it is usually fatal[55]. To our knowledge, our patients represent the first published cases of a second malignant neoplasm in the radiation field in patients with A-T, as well as the first published cases of a supratentorial PNET of the brain following cranial irradiation in individuals with A-T. It is intriguing that the brain tumors seen in these two patients appeared to be multifocal.

Patient 2 also experienced many other adverse effects of craniospinal irradiation, including leukoencephalopathy, growth hormone deficiency, precocious puberty, hypothyroidism, bilateral conductive hearing loss, and scoliosis. Leuko-encephalopathy has been described in children with A-T after prophylactic cranial irradiation[56] as well as in children without A-T.

Serum alpha-fetoprotein is a simple, rapid, and reliable screening test for A-T; it is elevated in more than 90% of A-T cases[1]. Cytogenetic studies reveal rearrangements involving chromosomes 7 and 14 in 5 to 15 percent of normal peripheral blood lymphocytes in individuals with A-T[57-59]. However, karyotyping can be technically difficult because the patients are often lymphopenic and the lymphocytes may not respond well to phytohemagglutinin (PHA). Confirmatory tests for A-T include the colony radio-sensitivity assay and identification of the ATM protein by immunoblotting[1,35,60-62]. These tests currently take three months to complete. DNA sequencing is usually not definitive because the full spectrum of ATM mutations has not yet been established and not all mutations are detected by any single laboratory platform[63]. A new flow cytometry-based assay that detects ATM kinase activity in peripheral blood mononuclear cells promises to shorten diagnostic testing to three days[64].

The range of neurological presentations of A-T is broad. Ataxia may be minimal or absent and the course seemingly non-progressive. The diagnosis of A-T should be considered in all children with neuromotor dysfunction or peripheral neuropathy, especially those who develop acute lymphoblastic leukemia, non-Hodgkin lymphoma or Hodgkin lymphoma. Radiation therapy and radiomimetic drugs such as bleomycin are best avoided in A-T patients with cancer[3,39,46,65]. The observations herein suggest that cranial irradiation may be especially dangerous. The need for a cooperative experience in the treatment of A-T patients who develop cancer is being addressed by the A-T Cancer Clinic at St. Jude Children's Research Hospital[24].

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