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Malignancies in pediatric patients with ataxia telangiectasia

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Abstract *Background.* Patients with ataxia telangiectasia (AT), known to have an inherent increased susceptibility to the development of cancer, may present with malignancies that are unusual for the patient's age, are often difficult to diagnose clinically and radiographically and respond poorly to conventional therapy.

Materials and methods. We reviewed the clinical presentation and imaging studies of 12 AT patients who developed malignancies.

Results. Eight of the twelve patients developed non-Hodgkin's lymphoma (CNS, thorax, bone), two developed Hodgkin's disease, and two were diagnosed with gastrointestinal mucinous adenocarcinoma.

Conclusion. The lymphomas were commonly extra nodal, and infiltrative rather than mass-like. The recognition of the tumors was often delayed due to confusion with the known infectious complications in AT patients.

Introduction

Patients with ataxia telangiectasia (AT), a rare immunodeficiency disorder, have an extraordinarily high incidence of developing a malignancy. The malignancies are predominately lymphoma, leukemia and tumors of the gastrointestinal tract [1].

A review of 12 pediatric patients with AT and cancer is presented to illustrate the variable nature of the malignancies, the difficulty in suggesting the diagnosis of cancer radiographically and the poor clinical outcome despite attempts with conventional therapy. Lymphomas, which represent the majority of the tumors [2, 3], were especially atypical from an imaging point of view. Recognition of the malignancies was often delayed due to confusion with the known infectious complications in AT patients.

Materials and methods

A retrospective study from four children's hospitals yielded 12 patients with ataxia telangiectasia and malignancy. The patients ranged in age from 3 years to 26 years (mean 10.3 years) at the time of cancer diagnosis. The clinical summaries and imaging studies were reviewed.

Results (Table 1)

Non-Hodgkin's lymphoma

Eight of 12 patients were diagnosed with non-Hodgkin's lymphoma. The non-Hodgkin's lymphoma cases were variable in presentation with predominately extranodal disease. Four patients are discussed in detail.

Table 1 Results

Case	Age/sex	Neoplasm	Site
1	12/F	Non-Hodgkin's lymphoma (B-cell)	Lung
2	26/F	Non-Hodgkin's lymphoma	Lung, L femur, CNS
3	10/M	Non-Hodgkin's lymphoma (T-cell)	Pleural and pericardial effusions
4	14/F	Non-Hodgkin's lymphoma	Stomach
5	3/F	Non-Hodgkin's lymphoma	Orbit
6	11/F	Hodgkin's lymphoma	Stomach, small bowel, liver, bone marrow
7	3/F	Hodgkin's lymphoma	Pharynx
8	6/M	Non-Hodgkin's lymphoma	CNS
9	4/M	Non-Hodgkin's lymphoma	CNS
10	13/M	Non-Hodgkin's lymphoma	Lung, mediastinum
11	15/F	Mucinous adenocarcinoma	Colon
12	17/F	Mucinous adenocarcinoma	Omentum

Case 1 (Fig. 1)

This patient, who had sinusitis and chronic lung changes from recurrent infections, developed a focal consolidation at the right lung base, which was initially thought to be infectious. The right lower lobe mass enlarged despite more than a month of antibiotics. A right lower lobectomy, partial right middle lobectomy and right axillary node excision were performed and pathology confirmed the presence of non-Hodgkin's B cell lymphoma.

Case 2

This patient, who also had many prior pulmonary infections, developed a cavitary lesion in the right lower lobe (Fig. 2), which was initially thought to be infectious. However, after tissue was obtained, the diagnosis of non-Hodgkin's lymphoma was made. Although this patient was diagnosed early in life with AT, the lymphoma presented at age 26. The patient also developed a destructive lesion of the femoral neck, as well as an extra-axial CNS mass with associated bony destruction before succumbing to her malignancy.

Case 3

A 10-year-old presented with 1 year of weight loss and neurologic deterioration. He was admitted with 1 week of dyspnea. The chest radiograph revealed complete opacification of the left hemithorax, and an echocardiogram demonstrated a large pericardial effusion. Analysis of pericardial and pleural fluid revealed T-cell lymphoma. The patient received chemotherapy and relapsed with CNS involvement 1.5 years later.

Case 4

This patient was a 14-year-old with abdominal pain, two episodes of hematemesis, moderate anemia and an elevated alpha-fetoprotein level. An abdominal CT (Fig. 3) demonstrated a thick stomach wall without evidence of adenopathy. An endoscopic biopsy revealed non-Hodgkin's lymphoma.

Three of the other non-Hodgkin's lymphoma cases involved the brain or orbit (case 5, Fig. 4).

Hodgkin's disease

Case 6

One of the two Hodgkin's disease cases proved especially difficult to diagnose. The presentation of persistent fever, weight loss and increasing weakness with associated leukopenia, ascites, and bilateral pleural effusions in this 11-year-old girl led to a search for an underlying infection or malignancy. A bone marrow biopsy and multiple blood cultures were negative. A CT scan of the abdomen revealed hepatosplenomegaly, lymphadenopathy, ascites and pleural effusions. CT gastric wall changes (Fig. 5) and mild small bowel fold thickening were also seen on the upper GI series (Fig. 6).

Initial liver biopsy and a repeat bone marrow biopsy were negative. During the hospital course, the patient started bleeding from the gastrointestinal tract and developed anemia, which required multiple blood transfusions. Upper endoscopy with biopsy and colonoscopy were unremarkable. A tagged red blood cell scan was positive in the small bowel during an episode of GI bleeding. A visceral angiogram was negative. An exploratory laparotomy revealed an ecchymotic small bowel with multiple telangiectasias. Repeat liver biopsy, bone marrow biopsy and resection of a small bowel lesion were performed at the time of laparotomy. Pathology of all of the specimens finally confirmed the presence of diffuse Hodgkin's disease.

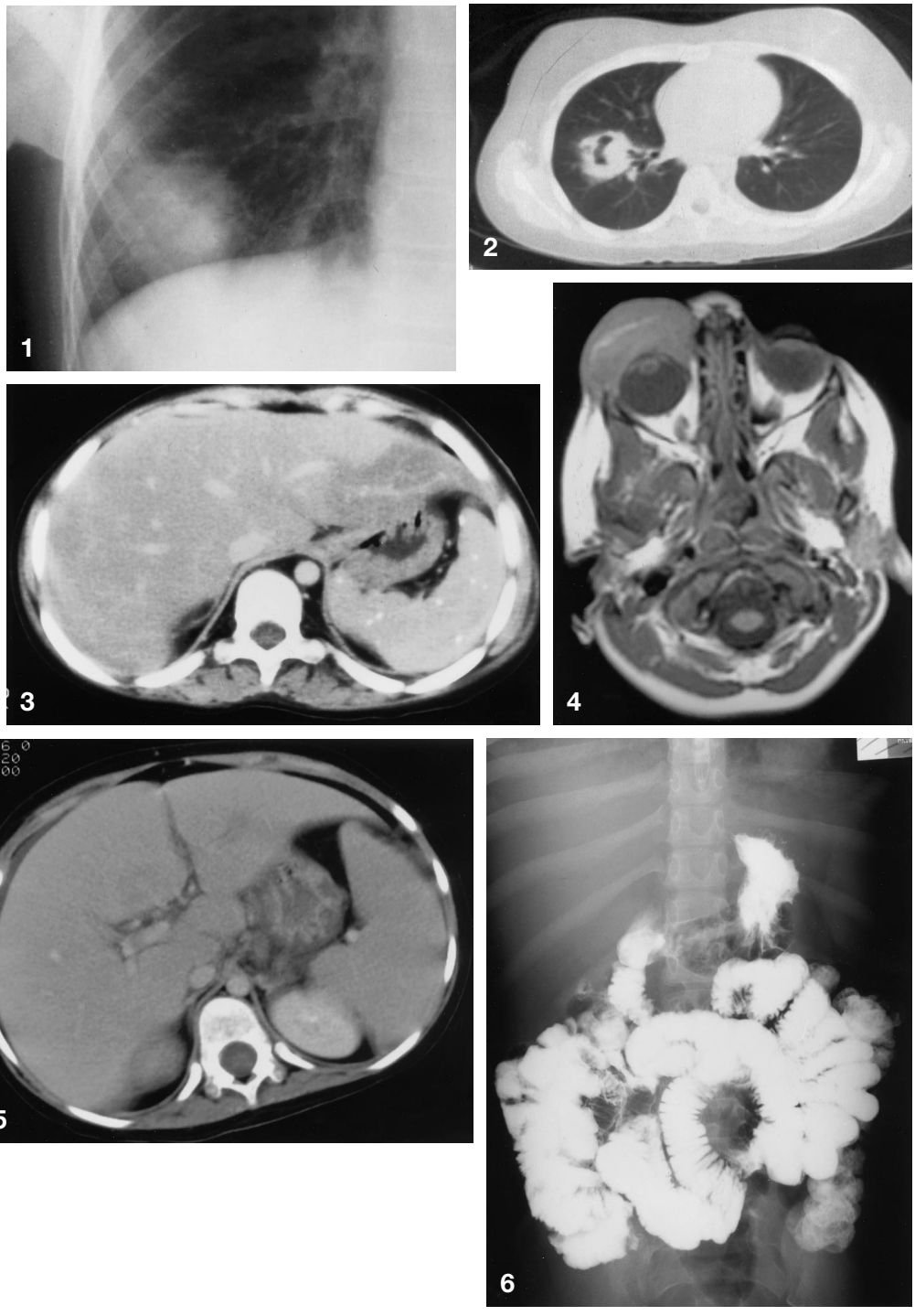


Fig. 1 (Case 1) Twelve-year-old girl with B-cell non-Hodgkin's lymphoma of the lung. Right lower lobe opacity thought initially to be infectious; mass unchanged with antibiotic therapy. Resection demonstrated tumor of the RLL with axillary nodal metastases

Fig. 2 (Case 2) Twenty-six-year-old woman with AT diagnosed at age 4. History of multiple sinopulmonary infections. CT of the chest with cavitary lung lesion; biopsy proven non-Hodgkin's lymphoma

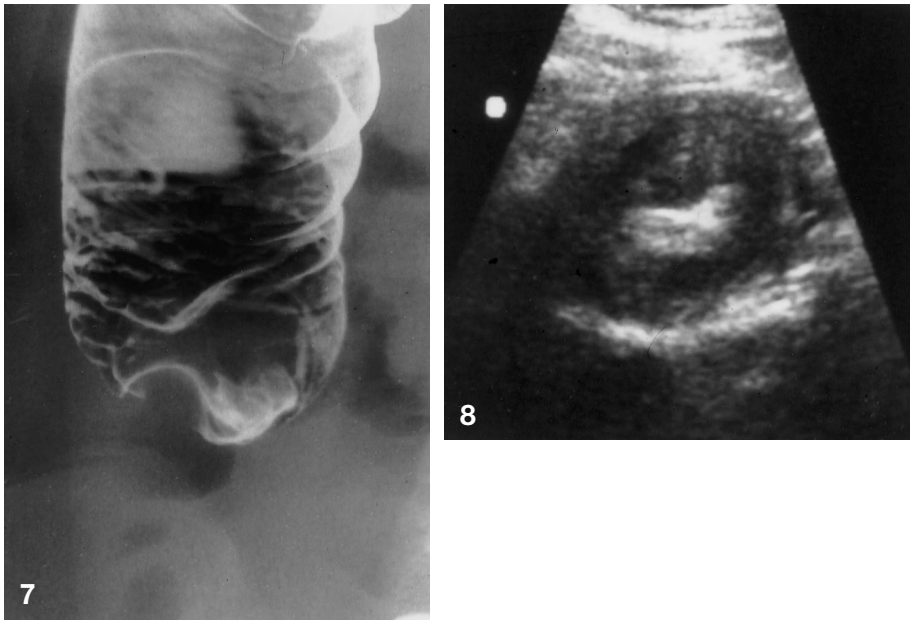
Fig. 3 (Case 6) Eleven-year-old girl with abdominal pain. Abdominal CT demonstrates thick-walled stomach. Splenic calcifications were secondary to previous histoplasmosis. Endoscopic biopsy of stomach led to diagnosis of non-Hodgkin's lymphoma

Case 7

This patient was diagnosed with Hodgkin's disease of the pharynx at age 3 before it was recognized that the patient had AT.

Fig. 4 (Case 5) Three-year-old girl. T1 axial MRI demonstrates large preseptal, extraconal soft-tissue mass involving the right orbit. Biopsy confirmed the diagnosis of non-Hodgkin's lymphoma

Figs. 5, 6 (Case 6) Eleven-year-old girl. CT and UGI demonstrate thick gastric rugal folds. Endoscopic biopsy of stomach failed to make diagnosis of lymphoma. Eventual open biopsy demonstrated diffuse Hodgkin's lymphoma of the GI tract



Figs. 7, 8 (Case 11) Fifteen-year-old girl. Barium enema shows cecal filling defect. The corresponding ultrasound demonstrates the typical appearance of an intussusception. Surgical findings confirmed the presence of a colocolic intussusception with adenocarcinoma of the colon as the lead point

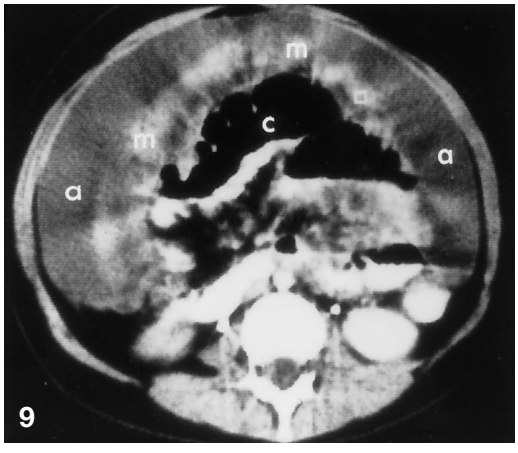


Fig. 9 (Case 12) Seventeen-year-old girl. CT scan of abdomen shows ascites and omental caking. The mucinous adenocarcinoma was presumed to be of gastrointestinal origin (*A* ascites, *M* masses in omentum, *C* colon)

Gastrointestinal adenocarcinoma

The two cases of mucinous adenocarcinoma of the gastrointestinal tract were in older patients (ages 15 and 17) compared to the majority of the lymphoma patients.

Case 11

This 15-year-old patient presented with iron-deficiency anemia and rectal bleeding. An upper GI and Meckel's scan were normal. A barium enema revealed a filling defect in the cecum that corresponded to an intussusception on ultrasound (Figs. 7, 8). At surgery, a 4×5 cm irreducible colocolic intussusception was found 10 cm distal to the cecum. Pathology was positive for mucinous adenocarcinoma of the colon. The patient died within a year with intra-abdominal metastases, ascites and a suspected sigmoid recurrence.

Case 12

This patient was a 17-year-old female with severe AT. She presented with abdominal pain, ascites and a right pleural effusion. An abdominal CT (Fig. 9) demonstrated ascites and omental caking. Metastases in the omentum were discovered at surgery, and pathology revealed metastatic mucinous adenocarcinoma, which was most likely of gastrointestinal origin. The patient died within 2 months of cancer diagnosis.

Discussion

Ataxia telangiectasia is a rare inherited immunodeficiency disorder with a wide range of clinical features, including progressive truncal ataxia, oculocutaneous telangiectasias, bronchopulmonary infections, cancer predisposition and radiation sensitivity. The inheritance of AT is autosomal recessive, i. e., mutated copies of the gene must be inherited from both parents. Most individuals suffering from the clinical syndrome are, in fact, complex heterozygotes rather than homozygotes since there are different mutations in the two alleles.

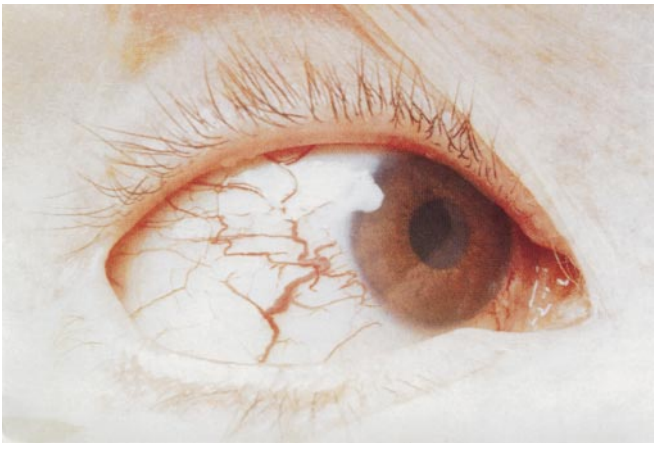


Fig. 10 Typical ocular telangiectasias often do not present until age 6–8 years old

The first clinical description of the disease was in 1926 by Syllaba and Henner and only later by Louis Bar in 1941 (in Europe, it is commonly referred to as the Louis Bar syndrome). Boder and Sedgwick described and named the disease "ataxia telangiectasia" in 1957–1958. Since that time, advances in molecular biology have led to the localization of the AT gene to the 11q 22–23 region in 1988 [4] and its sequencing in 1995 [5], when the gene was named ataxia telangiectasia mutated (ATM). It is a very large gene consisting of 150 kb. Some mutations resulting in the clinical syndrome appear to be random. It is very difficult to identify heterozygotes by screening.

Ataxia is almost always the presenting feature in children with AT, usually identified by the time the infant starts to walk. Telangiectasias (Fig. 10) often do not appear until the patients are 6 to 8 years old [6]. Other features include thymic hypoplasia, hypogonadism, growth retardation and defects in both cell-mediated and humoral immunity [7].

In the large cohort of 44 patients with AT studied longitudinally by Boder and Sedgwick, pulmonary disease was the commonest cause of death and cancer was second most common [8]. The immunodeficiency cancer registry (ICR) data include the types of malignancies reported in the AT patients. The largest class of malignancies consists of non-Hodgkin's lymphomas and leukemias (64 %), then other solid tumors (26 %) and Hodgkin's disease (10 %) [2]. The malignancies may *precede* the diagnosis of AT. Awareness of the underlying immunodeficiency disorder in these patients is crucial to identify due to the need to modify chemotherapy and radiation treatment protocols.

It has been recognized that individuals with primary or secondary immunodeficiencies have a significantly increased risk of both infection and malignancy. Other such syndromes include Wiskott-Aldrich (WAS), common variable immunodeficiency and severe combined immunodeficiency (SCID). The largest number of malignancies occur in patients with AT, followed by common variable immunodeficiency and WAS. According to the ICR, non-Hodgkin's lymphoma is the most common malignancy in all of these disorders [9].

The lymphomas in AT patients specifically are a very heterogeneous group of histologic subtypes. They are more similar in morphology and cell marker characteristics to lymphoma in non-immunodeficient children than the lymphomas in WAS and SCIDS [9].

Lymphoma in our AT patients was difficult to diagnose because of the extranodal predominance of disease and concurrent medical problems. In several cases, the imaging findings simulated the known infectious complications that these patients develop.

Clearly, if an ill child with a known diagnosis of AT is being seen, this should alert the pediatrician and radiologist to search for concurrent malignancy. Conversely, the child who presents with a malignancy atypical for the patient's age, tumor histology or tumor location should serve as a warning for the possibility of an underlying and undiagnosed immunodeficiency disorder. Since the AT gene is also associated with a cellular repair deficiency and therefore an unusual sensitivity to ionizing radiation, this information is crucial for modification of radiation protocols in these patients.

Patients with AT may develop devastating tissue necrosis after conventional radiotherapy exposure [10]. Even more interesting is the observation that cultured cells from AT patients are more sensitive to X-rays than control cells by a factor of 3. Since AT results from a germline mutation, all cells in the body including tumor cells carry this mutation. Consequently, the tumor cells are radiosensitized to roughly the same extent as normal tissues, so that patients may still be treated with radiation as long as lower doses are used. Although not within the scope of this paper, a debate currently exists whether heterozygotes with only one copy of the ATM gene are also radiosensitive and susceptible to cancer. Heterozygotes are estimated to be approximately 1 % of the U. S. white population [11]. A further study by Swift et al. suggested that AT heterozygotes are susceptible to radiation-induced cancer [12], although the data have been challenged as inadequate and have raised concern about the radiation exposure from mammography in these patients [3].

In conclusion, this report from four children's hospitals confirms many prior isolated case reports of malignancy in homozygous ataxia telangiectasia patients and shows the problems of diagnosis in such patients.

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