Ataxia Telangiectasia and Juvenile Idiopathic Arthritis

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We report, to the best of our knowledge, the first case of a child with typical ataxia telangiectasia (A-T) who developed juvenile idiopathic arthritis (JIA). The patient was a 15-year-old boy with A-T who presented with noninfectious polyarthritis. A-T is a rare, autosomal recessive disorder characterized by cerebellar atrophy, oculocutaneous telangiectasia, immunodeficiency, radiosensitivity, and predisposition to cancer. The gene responsible for A-T is the A-T mutated (*ATM*) gene. Clinical manifestations of the disorder are the result of lacking ATM protein, which is involved in DNA repair, apoptosis, various checkpoints in the cell cycle, gene regulation, translation, initiation, and telomere maintenance. There are a few articles that describe deficiency of the DNA repair enzyme, ATM, in rheumatoid arthritis, but the connection between the absence of ATM protein and JIA has not been presented or studied yet. JIA is a heterogeneous group of diseases characterized by arthritis of unknown origin with onset before the age of 16 years. It is the most common childhood chronic rheumatic disease and causes significant disability. Because immunodeficiency can be part of A-T, infectious arthritis can occur, but chronic autoimmune arthritis in these patients is rare. We report a rare case of a 15-year-old boy with A-T and JIA. This case shows a possible relationship between altered function of ATM protein and the pathogenesis of JIA.

Ataxia telangiectasia (A-T) is a rare neurodegenerative disorder with cerebellar ataxia as the prominent clinical feature, but mutation of the A-T mutated (*ATM*) gene can also lead to various immunologic and reproductive defects, extreme radiosensitivity, as well as a predisposition to cancer. A-T belongs to a group of DNA repair defects that affect DNA repair machinery.[1] Chronic articular involvement in those DNA repair defects is rare. In the literature, only 3 cases of noninfectious arthritis have been reported in patients with Nijmegen breakage syndrome and an atypical form of A-T.[2–4]

Juvenile idiopathic arthritis (JIA) has not been reported so far in a patient with typical A-T.

PATIENT PRESENTATION

Our boy patient was diagnosed with A-T by a neuropediatrician at the age of 1 year. At the age of 15 years, he presented to our pulmology, allergology, immunology, and rheumatology department with pain and swelling of his right ankle, right metatarsophalangeal, left first metacarpophalangeal, and interphalangeal joints that lasted for >2 months. The affected joints were swollen and warm, and he reported pain on active motion of his right ankle. He had no history of trauma and his family history was negative for primary immunodeficiencies and rheumatologic disorders. To exclude possible septic arthritis/osteomyelitis, we performed a bone scintigraphy,

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Dr Pasini conceptualized and drafted the initial manuscript; Dr Gagro conceptualized the initial manuscript and critically revised the manuscript; Dr Roić helped with the radiologic findings, making the diagnosis, and writing the initial manuscript and critically revised the manuscript; Dr Vrdoljak helped with the therapy and follow-up of the patient and writing the initial manuscript; Drs Lujić and Žutelija-Fattorini were involved in making the diagnosis, follow-up of the patient, and writing the initial manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: 10.1542/peds.2016-1279

Accepted for publication Sep 12, 2016

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: Pasini AM, Gagro A, Roić G, et al. Ataxia Telangiectasia and Juvenile Idiopathic Arthritis. *Pediatrics.* 2017;139(2):e20161279

which showed increased radiotracer uptake in soft tissues around various joints, especially around the right talocrural region (Figs 1 and 2). A radiograph of the right ankle and foot showed bone demineralization, swelling of the soft tissue around the right ankle, and narrowing of the tarsal joints with subchondral osteosclerosis (Fig 3). Laboratory investigation demonstrated a mild increase in acute phase reactants (erythrocyte sedimentation rate, 25 mm/h, C-reactive protein, 7.2 mg/L), lymphopenia (0.83×10^9/L), increased α-fetoprotein (256 μg/L), partial immunoglobulin A deficiency (0.56 g/L), decreased number of helper T cells ($CD3^+CD4^+$; 227/μL), and reduced lymphoproliferative responses to the mitogens, phytohemagglutinin and concanavalin A. Liver function tests, urinalysis, and other tumor markers were normal. Antinuclear antibodies, rheumatoid factor, cyclic citrullinated peptide antibodies, and HLA-B27 were all negative. We started therapy with the nonsteroidal antiinflammatory drug, indomethacin, with partial response. We then performed intraarticular injection of triamcinolone-hexacetonide of the right ankle and left first metacarpophalangeal joint. His right ankle responded well to the therapy, but the improvement in the first metacarpophalangeal joint was modest (Fig 4). After this treatment, disease activity in our patient as assessed by the Juvenile Arthritis Disease Activity Score-10,[5] which comprises 4 variables (physician global assessment, parent/patient global assessment, active joint count, and acute-phase reactant), changed from an initial score of 30.5 to 6.

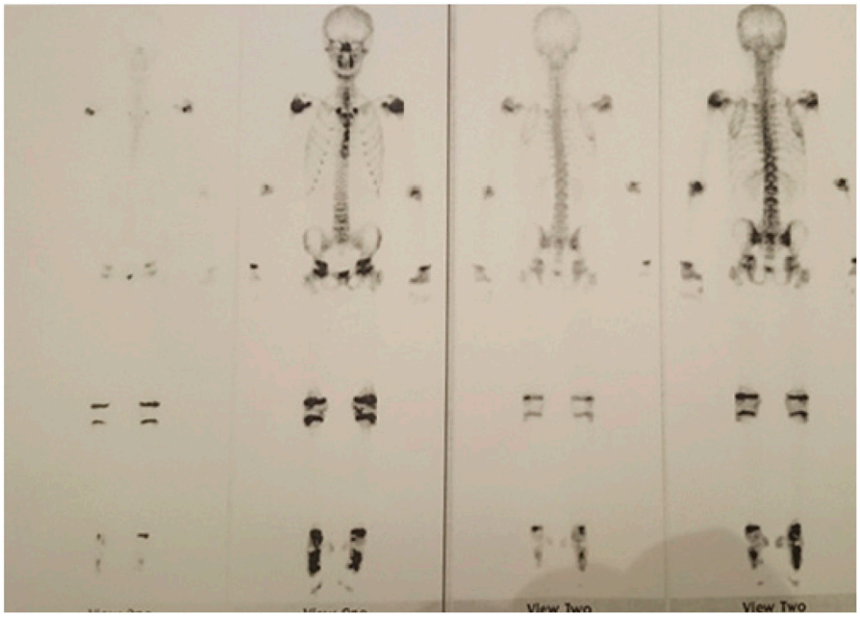

FIGURE 1
Bone scintigraphy, delayed phase; increased uptake of radiopharmaceutical in soft tissue around the right talocrural region.

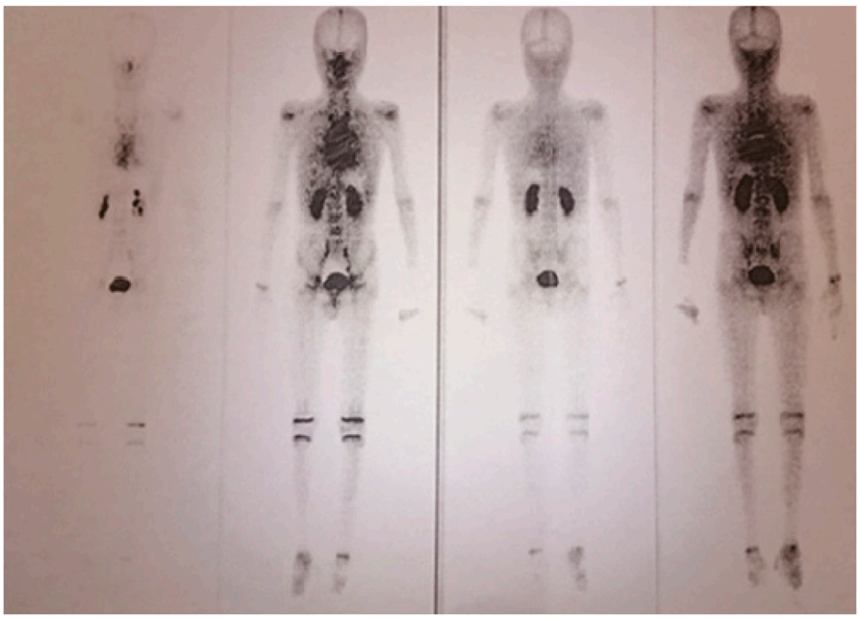

FIGURE 2
Bone scintigraphy, blood pool image; increased uptake of radiopharmaceutical in soft tissue around the right talocrural region.

DISCUSSION

JIA is an autoimmune disease that is considered to be a consequence of the combination of genetic susceptibility and unknown environmental triggers leading to activation of both innate and adaptive immunity that causes tissue damage.[6] A-T is also called progeroid syndrome due to the role of ATM protein in telomere maintenance. Namely, ATM mutation leads to accelerated telomere loss, which causes impaired proliferation and premature senescence of cells.[7] Premature aging of the immune system, which is associated with telomere dysfunction and premature T cell senescence, has been reported in children with JIA and adults with

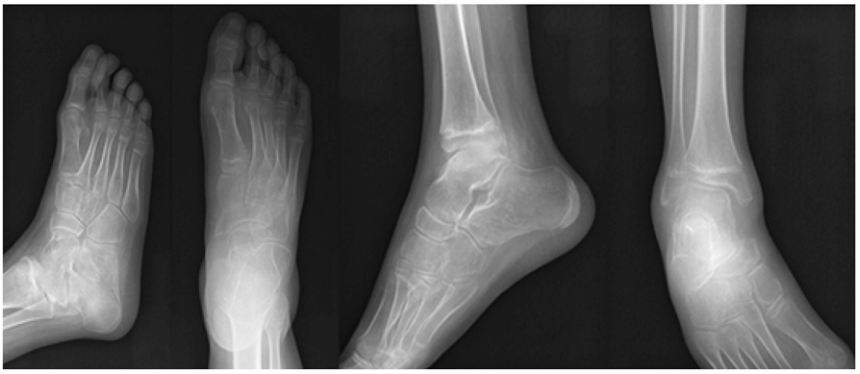

FIGURE 3
Radiograph of the right ankle and foot; bone demineralization, swelling of the soft tissue around the right ankle, and narrowing of the tarsal joints with subchondral osteosclerosis.

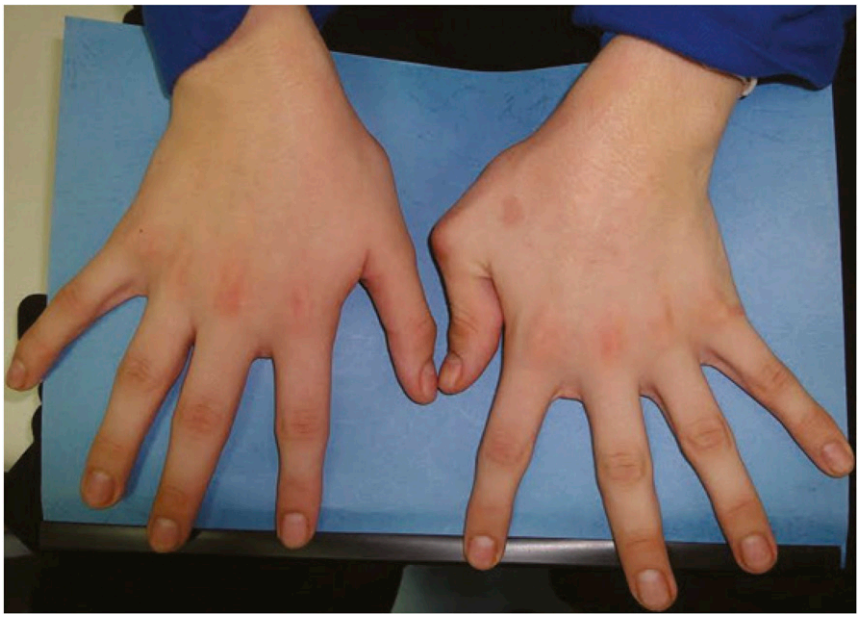

FIGURE 4
Arthritis of the first metacarpophalangeal joint.

rheumatoid arthritis.[8–11] In the literature, only 1 case of a 9-year-old girl with an atypical form of A-T and an additional de novo 3.14-Mb microduplication in region 19q12, who developed JIA, has been reported.[4] Arthritis has also been described in a pediatric patient with Nijmegen breakage syndrome, which is also a rare autosomal recessive DNA repair disorder caused by hypomorphic mutations of the *NBS1* gene.[2,3] To our knowledge, there are no published studies on the association of ATM deficiency and JIA. In contrast, adults with rheumatoid arthritis have an accumulation of DNA strand breaks with associated sensitivity to apoptosis due to repressed production of transcripts and ATM protein as well as other molecules involved in DNA repair pathways.[12]

Immunodeficiency does not affect all A-T patients; some have no infections and normal immunologic investigations. When present, the immunodeficiency may affect the humoral immune system, cellular immune system, or both, and present a risk for increased incidence of infections.[13] Therefore, in a patient with A-T who presents with arthritis, it is mandatory to exclude an infectious origin first, as we did for our patient.

Laboratory evaluation of our patient, who presented with chronic noninfectious arthritis, was not positive for common rheumatologic tests, such as antinuclear antibodies, rheumatoid factor, and HLA-B27 tests. However, it should be stressed that these tests help us to exclude other underlying disorders, classify the type of arthritis, and evaluate for extraarticular manifestations of JIA.[6]

The association of primary immunodeficiency syndromes, such as humoral and complement immunodeficiencies, and various autoimmune diseases are well known. Cunningham-Rundles and Bodian[14] described 4 patients with common variable immunodeficiency and JIA in their cohort, which included 248 patients ranging in age from 3 to 79 years who had been followed for a period of 1 to 25 years.

However, autoimmune diseases, including JIA, are generally considered to have a polygenic inheritance pattern. Based on mounting evidence for the role of several different monogenic defects associated with primary immunodeficiencies and autoimmune phenotypes, we should be aware of the possibility that altered function of ATM gene might contribute to the development of chronic arthritis.[15]

Our patient responded well to therapy with intraarticular corticosteroid and indomethacin and was in remission during follow-up at our outpatient clinic for 2 years. He was transferred to adult-oriented health care when he reached 18 years of age. A close monitoring of his disease was agreed to at transfer to recognize early any signs of disease relapse. The susceptibility of A-T patients to cancer, especially lymphoma, however, might limit

the usage of other drugs that are recommended for treatment of juvenile-onset arthritis, such as methotrexate and anti-tumor necrosis factor agents, in case of a relapse of arthritis.

CONCLUSIONS

If a patient with A-T develops arthritis, a diagnosis of JIA should be considered. We report, to the best of our knowledge, the first case of a child with typical A-T who developed JIA. In the future, it will be interesting to investigate if ATM deficiency plays a role in the pathogenesis of JIA.

ABBREVIATIONS

A-T: ataxia telangiectasia
ATM: ataxia telangiectasia mutated
JIA: juvenile idiopathic arthritis

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Pediatrics 2017;139;
DOI: 10.1542/peds.2016-1279 originally published online January 12, 2017;

PEDIATRICS®
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