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PICTORIAL ESSAY

Imaging findings of mixed connective tissue disease in children and adolescents: a case series

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Abstract

Mixed connective tissue disease (MCTD) is a rare disease in children and adolescents which overlaps features of juvenile idiopathic arthritis, polymyositis/dermatomyositis, systemic lupus erythematosus, and systemic sclerosis. We have provided an image-based approach for evaluation of MCTD in children and adolescents, outlying the most frequent imaging findings. This approach would aid imagers and clinicians to consider the diagnosis of this rare entity and be able to make an accurate list of differential diagnosis for complex rheumatologic diseases such as MCTD, thus facilitating the ultimate goal of early diagnosis and optimal management of affected children.

Keywords Mixed connective tissue disorder · Children and adolescents · Differential diagnosis · Imaging · Juvenile idiopathic arthritis · Polymyositis/dermatomyositis · Systemic lupus erythematosus · Systemic sclerosis

Introduction

Mixed connective tissue disease (MCTD) is a rare autoimmune disease in children and adolescents that overlaps features of juvenile idiopathic arthritis (JIA), polymyositis/dermatomyositis (PM/DM), systemic lupus erythematosus (SLE), and systemic sclerosis (SS). Clinical characteristics of this entity encompass more than one disease or remain undifferentiated and involve few features from different rheumatic diseases [1, 2].

Polyarthritis is the most common initial presentation of MCTD in children and adolescents, where arthritis/arthropathic changes can be assessed on plain films [2]. However, magnetic resonance imaging (MRI) provides more information about inflammatory processes involving the bone marrow, soft tissue, and muscles.

Commonly, the gastrointestinal tract is involved leading to gastroesophageal reflux (GER), esophageal dysmotility, or delayed emptying of stomach which can often be demonstrated using fluoroscopic studies [1, 2]. Nephritis is the most frequent abdominal manifestation as well as hepatomegaly and splenomegaly [2]. Children with MCTD may tend to have alterations of blood count rather than multiorgan involvement. Early signs of pulmonary involvement are often missed on chest radiographs. High-resolution computed tomography (HRCT) is the method of choice for the assessment of acute and chronic parenchymal and interstitial lung changes cross sectionally and overtime [2].

Presently, there is no consensus for unique classification criteria for pediatric MCTD [3–5]. Nevertheless, the presence of specific antibodies to nuclear protein in the serum such as high titers of anti-uridine-rich RNA–small nuclear ribonucleoprotein (RNP), anti-U1-RNP antibodies, is a common criterion used in the most common classification systems for MCTD. The Alarcon-Segovia classification system has been reported as being the most sensitive and specific system for diagnosis of MCTD [5] and was utilized for classifying the cases presented in this essay. We describe the clinical-imaging findings of a series of cases of MCTD in children and adolescents of a single institution.

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Table 1 Demographic characteristics, clinical and imaging presentation of children and adolescents with mixed connective tissue disorders diagnosed at Sick Kids, Toronto, Canada from 1999 to 2017

Patients	Age (year)	Year of diagnosis	Initial presentation	Initial anti-RNP/anti dsDNA/anti SM/RF	Imaging body part involvement	Follow-up imaging/year	Imaging follow-up discrepancy	Clinical follow-up/last seen year
1	12	2001	Raynaud syndrome, myositis, arthritis, abnormal nail folds, suspected Gottrons, heliotropic rash	Strongly +/−/+/−	Hands–wrists, right SI–hip, kidney, GIS	Hands–wrists/2006	Worsening	Doing well + no Raynaud/2008
2	16	2000	Scleroderma, progressive muscle weakness, Raynaud syndrome	Strongly +/−/−/−	GIS	N/A	N/A	Doing well-ongoing Raynaud syndrome/2000
3	11	1998	Juvenile dermatomyositis, and turns into systemic scleroderma, fibromyalgia, sclerodactyly	Strongly +/−/−/−	Hands–wrists, lungs	Hands–wrists–lungs/2006	Worsening improvement	Ongoing stiffness + chronic pain/2009
4	15	2004	Polyarthritis, morning stiffness	Strongly +/−/−/−	Lung, shoulder and pelvic girdle muscles	Lungs/2005	Improvement	Doing well/2007
5	11	2003	Polyarthritis, myositis, sclerodactyly, GER, lung disease with decreased PFT	Strongly +/−/−/−	Hands–wrists, lungs	N/A	N/A	Doing well/2007
6	12	2000	Polyarthritis, starts like JIA and turns into overlap	Strongly +/+/+/−	Hands–wrists, ankles, bilateral TMJs, left hip, pelvic and proximal thigh muscles, lungs, spleen, GIS	Hands–wrists–lungs/2005	Worsening	Doing well/2006
7	16	2005	Raynaud syndrome, arthritis	Strongly +/−/−/−	Hands–wrists	N/A	Stable	Ongoing Raynaud syndrome/2007
8	14	2006	Stiffness, joint pain	Strongly +/−/−/−	Right ankle	N/A	N/A	Limitation of ROM of wrists/2008
9	15	2004	Joint pain/swelling, Raynaud syndrome,arthritis, dysphagia, sicca, chronic cough	Strongly +/−/−/−	GIS	N/A	N/A	Chronic pain, sicca, chronic cough, dysphagia, heartburn, Raynaud syndrome/2005

Table 1 (continued)

Patients	Age (year)	Year of diagnosis	Initial presentation	Initial anti-RNP/anti dsDNA/anti SM/RF	Imaging body part involvement	Follow-up imaging/year	Imaging follow-up discrepancy	Clinical follow-up/last seen year
10	11	2009	Raynaud syndrome, puffy fingers	Strongly +/−/−/−	Right hip, bilateral TMJs, GIS	Bilateral TMJs/2011	Improvement	No new-additional finding/2015
11	16	2009	JIA, joint pain, puffy fingers, Raynaud syndrome	Strongly +/−/−/−	Hands–wrists, CNS (right VII. nerve palsy)	N/A	N/A	Ongoing chronic pain/2010
12	14	2007	Arthritis, bilateral TMJs, Raynaud syndrome, sclerodactyly	Strongly +/−/−/−	Bilateral TMJs, liver	Bilateral TMJs/2011	Worsening	2012/No new-additional finding, ongoing Raynaud syndrome
13	10	2015	Inflammatory arthritis	Strongly +/−/−/−	N/A	N/A	N/A	2017/No new-additional finding, ongoing Raynaud syndrome
14	12	2017	Puffy fingers, stiffness, joint pain, tight skin, Raynaud syndrome, scleroderma	Strongly +/+/+/+	CNS (acute ischemic changes with multiple chronic ischemic insults in the bilateral deep white matter and basal ganglia)	N/A	N/A	2017/No new-additional finding, ongoing Raynaud syndrome

CNS central nervous system, *GIS* gastrointestinal system, *TMJ* temporomandibular joint, *ROM* range of motion, *NA* not applicable

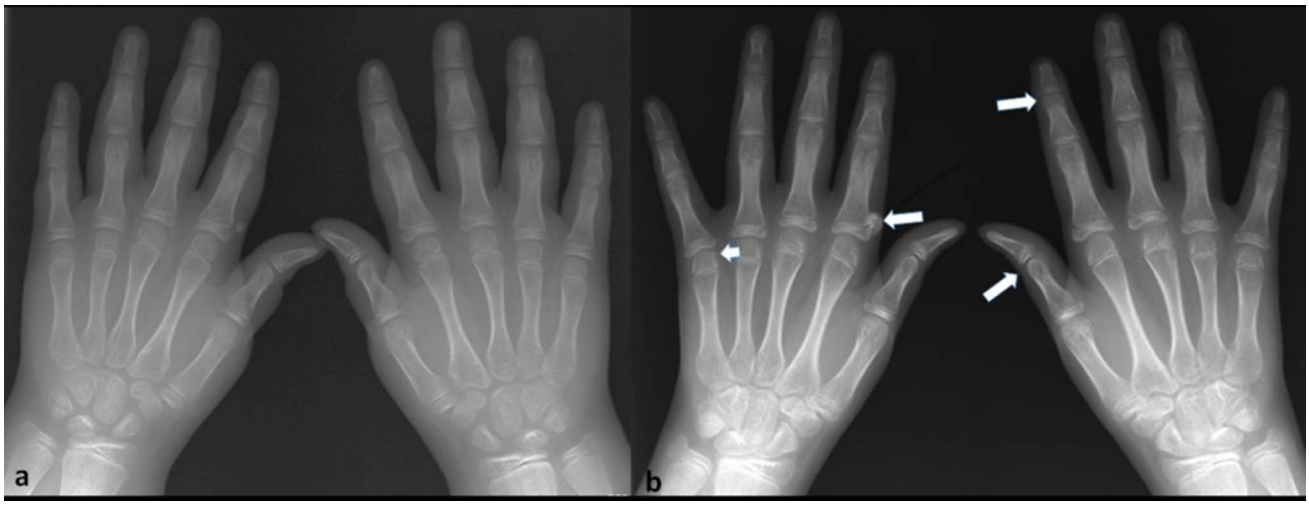

Fig. 1 Patient 3: plain films of the both hands demonstrate progression of mild periarticular osteopenia particularly with juxta-articular calcifications, particularly involving the radial aspect of the soft tissues adjacent to the 2nd metacarpophalangeal (MCP) on the left (arrow), 5th MCP on the left (arrow), 2nd tuft on the right (arrow), and on the right thumb (arrow) after 3 years. In addition, there appears to be resorption of the bony tufts of the 2nd digits as well. Soft-tissue tapering is seen of the fingers, greater on the right hand than the left

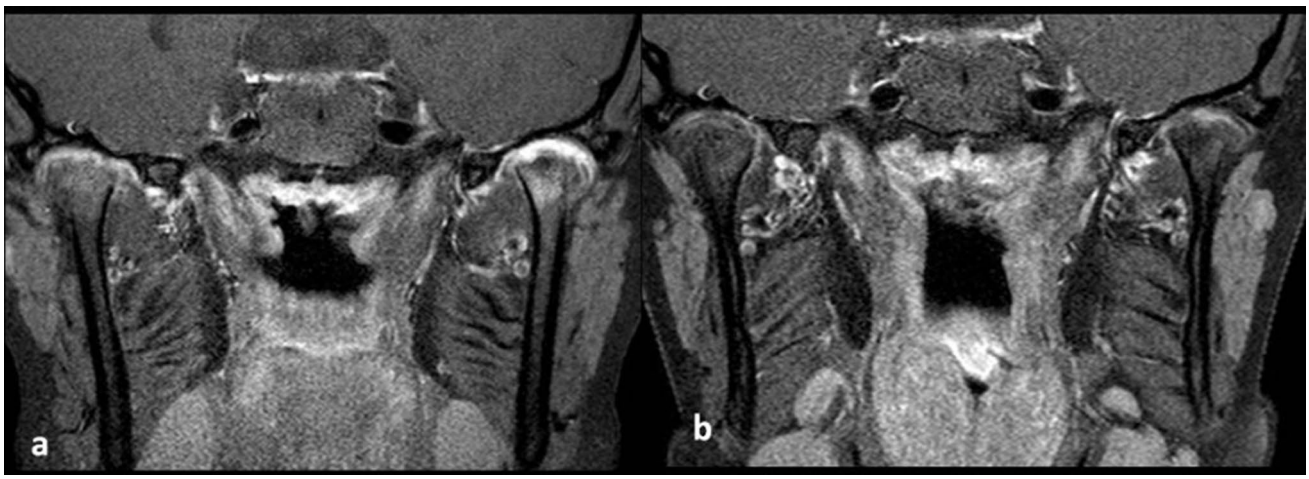

Fig. 2 Patient 10: coronal postcontrast fat-saturated T1-weighted MR images show flattening of both mandibular condyles with irregular outline and erosions (**a, b**). Compared to previous MRI (**a**), there was improvement of the bone marrow edema bilaterally with evidence of less contrast enhancement noted in both joint spaces (**b**) in 2 years

Presentation of cases

Cases for this pictorial essay were searched through the Pediatric Rheumatology and Radiology reporting databases of The Hospital for Sick Children (Sick Kids), Toronto, Canada during the time period from January 1, 1999 to April 20, 2017.

The diagnostic criterion for this search included high titers of anti U1-ribonucleoprotein (anti U1-RNP) antibodies and clinical and laboratory findings of other systemic disorders, such as JIA, PM/DM, SLE, SS, that corresponded to MCTD. Presently, there is no consensus for one classification criteria for pediatric MCTD yet [6]. High anti-U1-RNP titer was the common criterion utilized for the inclusion of patients in this pictorial essay.

We described the most frequent imaging features and provided a summary of pattern changes in different body systems cross-sectional and over time (Table 1). Imaging features were evaluated on radiography, fluoroscopy, abdominal ultrasound (US), chest CT, and MRI.

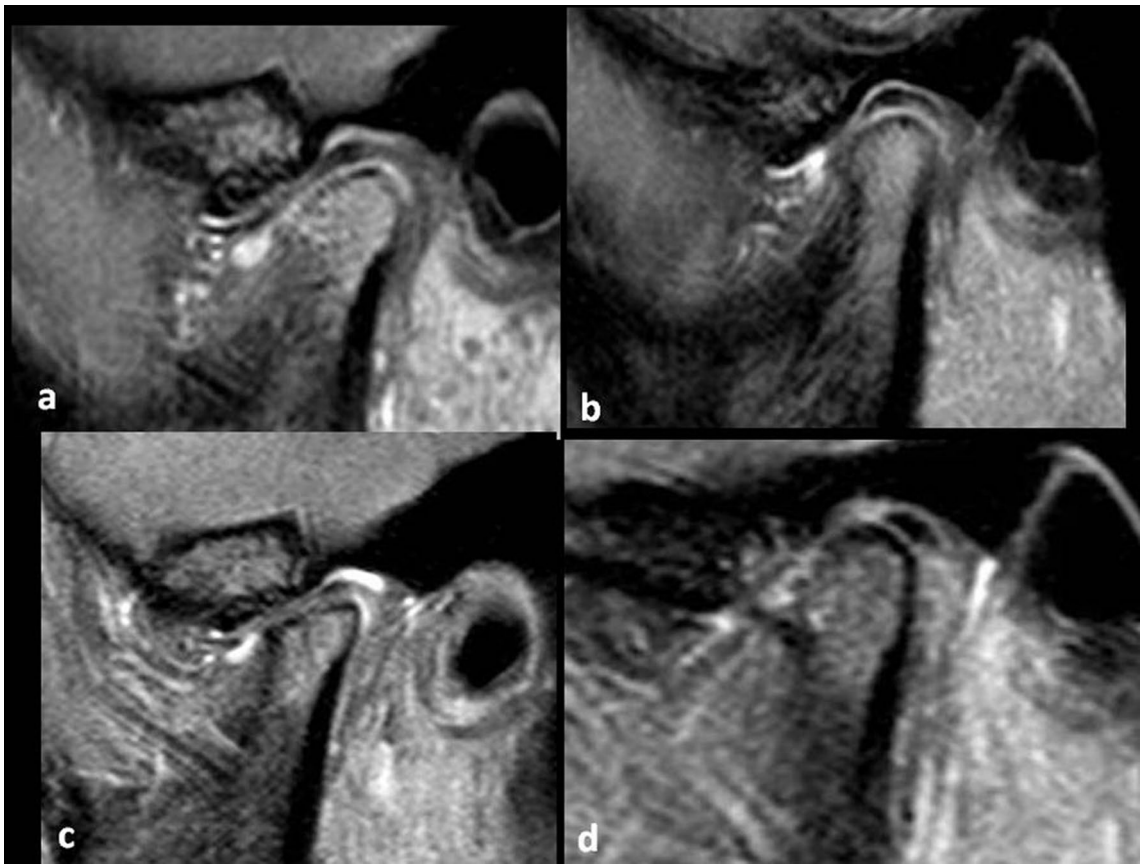

Fig. 3 Patient 12: sagittal post contrast fat saturated T1-weighted MR images (**c, d**) demonstrate worsening of arthritis including flattening of bilateral mandible condyles with irregular articular margins compared to previous MRI (**a, b**) in 1 year

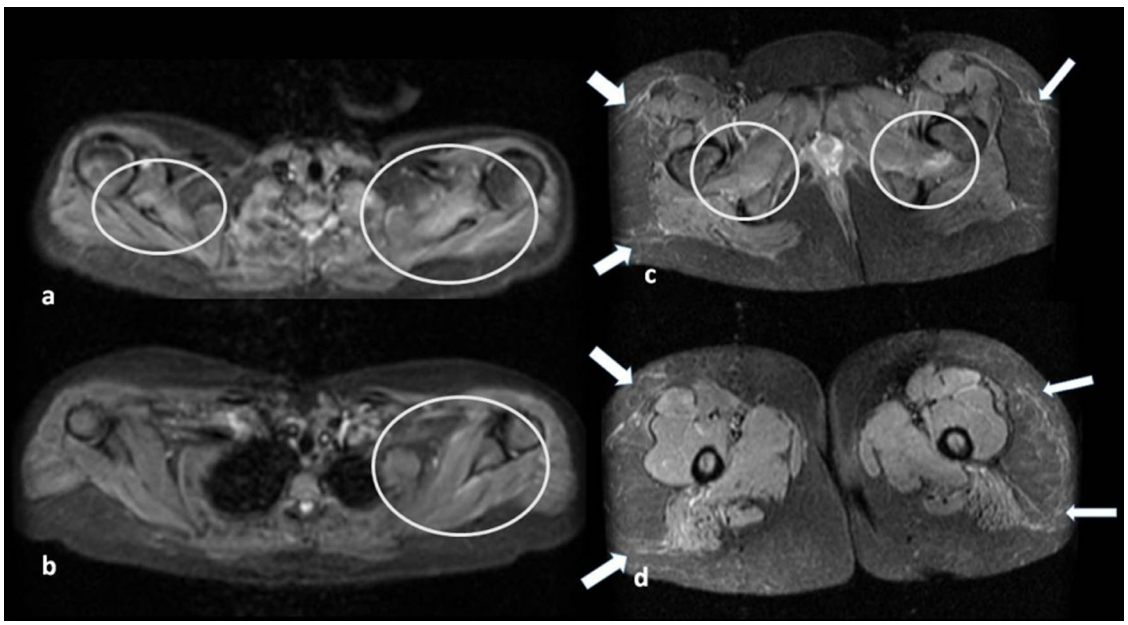

Fig. 4 Patient 10: axial short tau inversion recovery (STIR) images through shoulder and pelvic girdle demonstrate increased signal intensity involving both shoulder girdle muscles (**a, b**) (circles) in keeping with myositis. Focal abnormal high signal intensity in both adductor magnus muscles (circles) (**c**), which is more prominent on the left, associated with high signal on STIR sequences in the subcutaneous soft tissue in keeping with edema (arrows) (**d**)

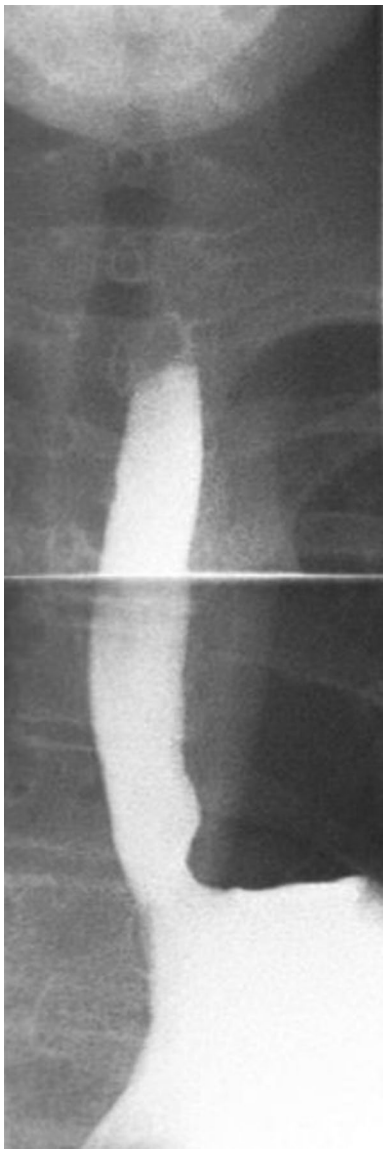

Fig. 5 Patient 1: upper GI fluoroscopy study with Barium demonstrates moderate amount of gastroesophageal reflux to the level of the upper to mid esophagus

Musculoskeletal findings

The most common clinical features of patients of this series were polyarthritis, polyarthralgia, puffy fingers, Raynaud phenomenon, and myositis. Hands metacarpophalangeal (MCP), proximal interphalangeal (PIP), distal interphalangeal (DIP), wrists, knees, elbows, shoulders, ankles, metatarsophalangeal (MTP), TMJ, and hips were reported to be the most common joints involved [2–5]. The arthritis in MCTD has been reported to be more erosive and/or deforming in adults than in children presenting with juxta-articular calcification, terminal tuft lysis, and edema of the hands [1–5]. However, we observed mild-to-moderate erosive or deforming arthritis/arthropathic changes in some of our patients on radiographic follow-up (Figs. 1, 2, 3).

Muscle involvement can involve muscles of the peripheral skeleton and organs of the gastrointestinal tract. Myositis or esophageal dysmotility are both characteristically mild at onset and may be associated with normal or elevated muscle enzymes [2]. Decreased physical function, proximal muscle weakness, and GER disease are the most common presentations [2]. The cutaneous, subcutaneous, and high signal muscular abnormalities on fat-saturated T2-weighted MR images, involving the shoulder and pelvic girdles, and proximal thigh muscles were concordant with inflammatory myositis as the initial clinical presentation (Fig. 4). Abnormal motility of esophagus, GER, vallecular–laryngeal pooling and penetration, and slow gastric emptying were demonstrated as a consequence of the muscle gastrointestinal involvement on fluoroscopy studies (Fig. 5).

Pulmonary findings

Pulmonary involvement in the pediatric population is less likely severe [2]. Aaløkken et al. showed discrete interstitial lung disease in 6/24 (25%) patients and only 1/24 (0.4%) patient had mild involvement [7]. These authors also described the most common CT features of pulmonary involvement in their case series such as microcystic and fine intralobular pulmonary changes [7]. Pulmonary involvement is non-specific and is comprised of findings seen in other connective tissue diseases; therefore, the diagnosis of MCTD is based on other pulmonary criteria [2, 7]. Ground-glass opacity, septal thickening and subpleural honeycombing are the most common CT findings reported in adult MCTD and often a complication of pulmonary hypertension [2]. Pulmonary fibrosis is the most common cause of morbidity and mortality in adult patients [2]. Patients show improvement or progression of pulmonary function correlated with severity of pulmonary fibrosis. The most common pulmonary findings encountered in our series were reticular lung changes, interlobular septal thickening, nodules, and ground glass opacity (Figs. 6, 7).

Abdominal findings

The most common abdominal characteristics of MCTD in children involve organomegaly of kidneys, liver, and spleen [1]. Renal involvement is reported less frequently but more severely in children than in adults. Organomegaly and increased echogenicity of the renal cortex which are non-specific ultrasound findings can be considered as abdominal manifestations in this population. Patients may also have associated hematologic problems including iron deficiency

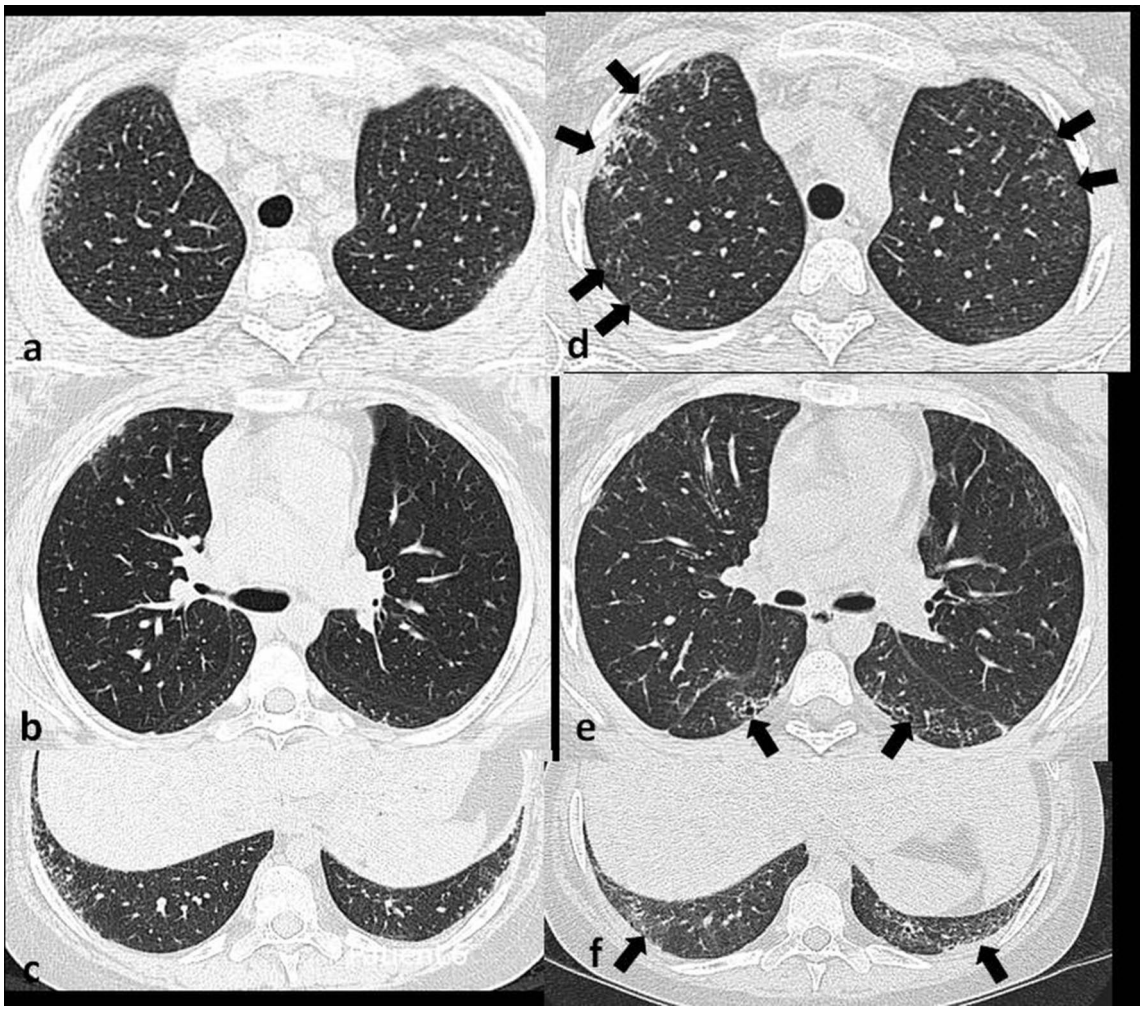

Fig. 6 Patient 6: axial high-resolution computed tomography (HRCT) images from prior (**a–c**) and follow-up (**d–f**) demonstrate progression of multifocal subpleural fibrotic changes with subpleural thickening in anterior segment of both upper lobes, more prominent on the right and apical segment and posterolateral area of both lower lobes (arrows) (**d**) in 4 years. Traction bronchiectasis changes are seen in the apical segments of both lower lobes, but more prominent on the right side (black arrows) (**e**). There is pleural thickening with pleural effusion in posterobasal segment of left lower lobe (arrows) (**f**)

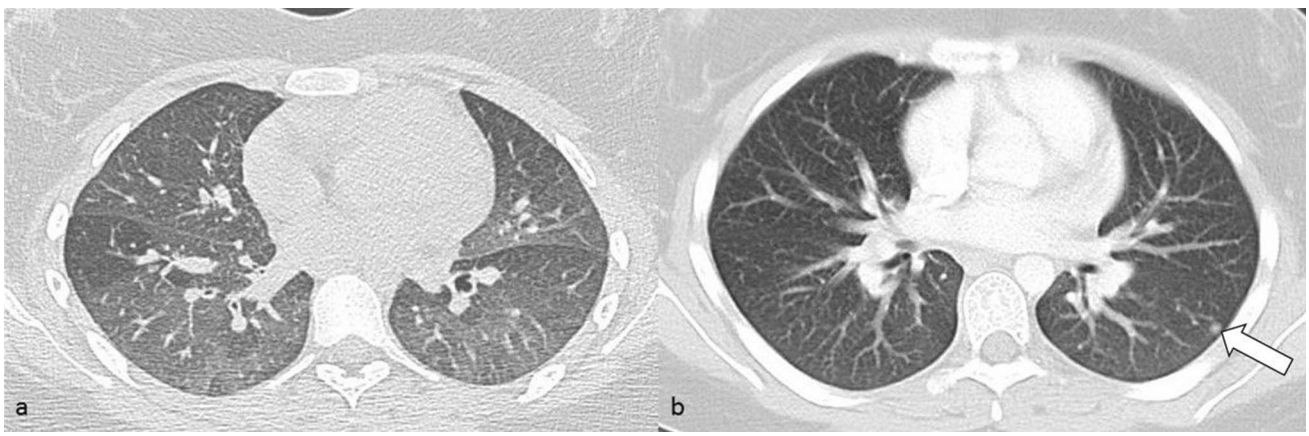

Fig. 7 Patient 4: resolution of the extensive ground glass opacities in bilateral lungs with associated nodular opacity within the superior segment of the left lung lower lobe on prior (**a**) and follow-up (**b**) (arrow) axial HRCT images in 1 year

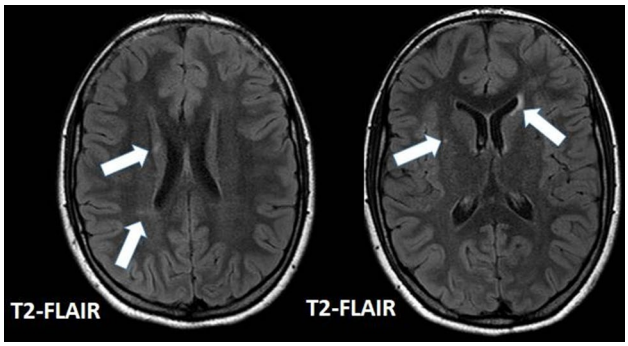

Fig. 8 Patient 14: T2-weighted/FLAIR hyperintense remote ischemic changes in bilateral periventricular white matter and head of right caudate with tiny chronic ischemic insults (white arrows)

anemia, leukopenia, and thrombocytopenia in addition to findings of autoimmune hepatitis [2].

Central nervous system findings

Central nervous system manifestations include neurological and psychiatric symptoms. Headache, seizures, hallucinations, trigeminal sensory neuropathy, and sensorineural hear loss are the most characteristic reported features overall. However, distinct central neural system (CNS) features of the most common MCTD-related rheumatic diseases can occur such as trigeminal and peripheral neuropathy in patients with scleroderma features, and optic neuropathy in patients with prominent SLE features [8, 9]. Patients with CNS manifestations presented with facial nerve palsy that had prominent scleroderma features initially. Patient with ischemic brain lesions on brain MRI presented with prominent SLE features (Fig. 8). Since CNS vasculitis due to connective tissue disease involvement may manifest ischemic changes within the brain, brain MRI is a method of choice for this patient group [1, 2]. We should acknowledge the fact that the dominance of scleroderma features in patients with MCTD may be associated with radiologic features of neuropathy, while dominance of SLE features may be associated with features of CNS vasculitis.

Conclusion

Imaging plays an important role in depicting and monitoring children and adolescents with MCTD. This is one of the few reports in the literature that characterize the musculoskeletal, pulmonary, gastrointestinal, and CNS manifestations of childhood MCTD as a reference-imaging tool. MCTD represents an overlap of several rheumatic diseases and the imaging features often correspond to the most dominant underlying condition. In the provision of an image-based approach for evaluation of MCTD in children, this report

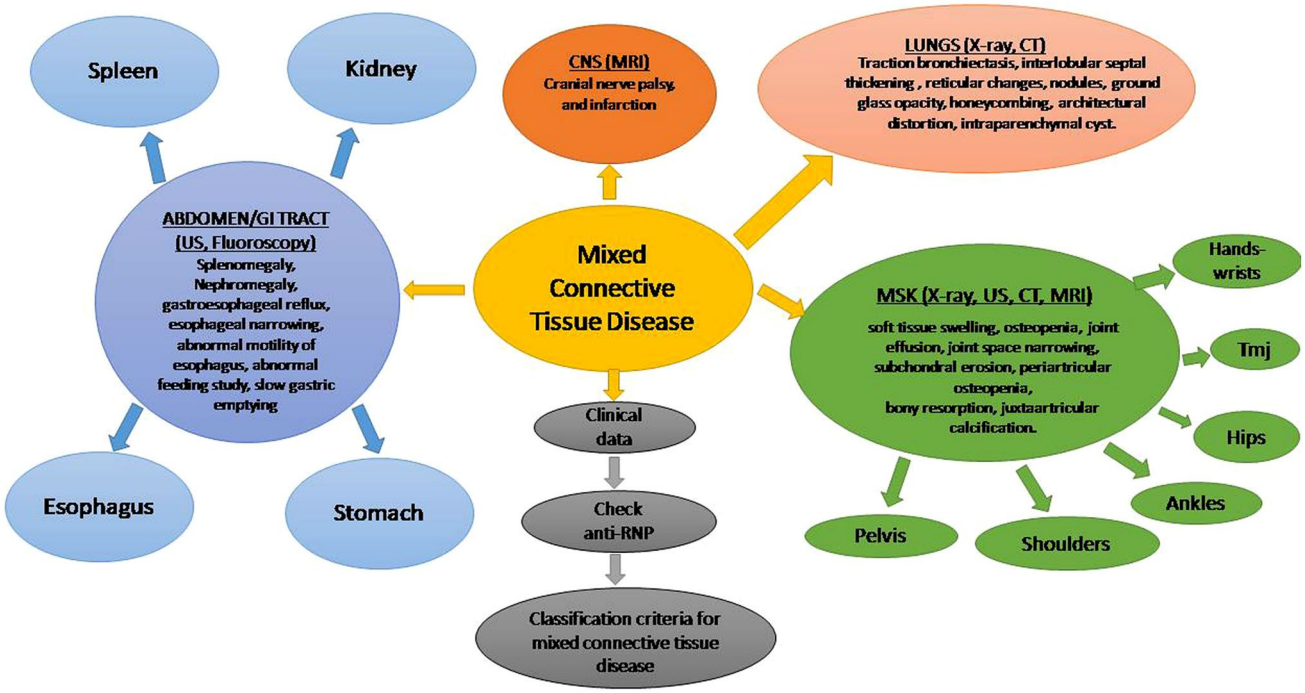

Fig. 9 Summary of multisystem imaging findings of pediatric mixed connective tissue disorder (MCTD)

may help imagers and clinicians to consider the diagnosis of this rare entity at its early presentation and to be able to consider an accurate list of differential diagnosis for complex rheumatologic diseases such as MCTD. This should facilitate the ultimate goal of early diagnosis and optimal management of affected children (Fig. 9).

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Compliance with ethical standards

Conflict of interest Authors declare that there is no conflict of interest.

Ethical statement This study was approved by the local ethical committee of The Hospital for Sick Children.

References

1. Petty RE, Lindsley CB, Laxer RM. The textbook of pediatric rheumatology. 7th ed. Philadelphia, PA: Elsevier; 2015. p. 418–20.
2. Berard RA, Laxer RM. Pediatric mixed connective tissue disease. Curr Rheumatol Rep. 2016;18:28.
3. Kahn MF, Appelboom T. Syndrome de Sharp. In: Kahn MF, Peltier AP, Mayer O, Piette JC, editors. Les maladies systemiques. 3rd ed. Paris: Flammarion; 1991. p. 545–56.
4. Sharp GC. In: Kasukawa R, Sharp GC, editors. Mixed connective tissue diseases and anti-nuclear antibodies. Amsterdam: Excerpta Medica; 1987. p. 23–32.
5. Alarcon-Segovia D, Villarreal M. In: Kasukawa R, Sharp GC, editors. Mixed connective tissue disease and anti-nuclear anti-bodies. Amsterdam: Excerpta Medica; 1987. p. 33–40.
6. Amigues JM, Cantagrel A, Abbal M, Mazieres B. Comparative study of 4 diagnosis criteria sets for mixed connective tissue disease in patients with anti-RNP antibodies. Autoimmunity Group of the Hospitals of Toulouse. J Rheumatol. 1996;23:2055–62.
7. Aaløkken TM, Lilleby V, Søyseth V, Mynarek G, Pripp AH, Johansen B, Førre O, Kolbenstvedt A. Chest abnormalities in juvenile-onset mixed connective tissue disease: assessment with high-resolution computed tomography and pulmonary function tests. Acta Radiol. 2009;50:430–6.
8. Hamoir B, Giroux M, Outteryck O, et al. Mixed connective tissue disease presenting as trigeminal neuropathy. Acta Neurol Belg. 2014;114:245–6.
9. Gal Y, Twig G, Mozes O, Greenberg G, Hoffmann C, Shoenfeld Y. Central nervous system involvement in systemic lupus erythematosus: an imaging challenge. Isr Med Assoc J. 2013;15:382–6.