The perils of myositis mimickers with illustrative case reports

I. Marago[1], J.B. Lilleker[1,2], H. Chinoy[2,3,4]

[1]Manchester Centre for Clinical Neuroscience, Manchester Academic Health Science Centre, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Salford, UK; [2]National Institute for Health Research, Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, The University of Manchester, UK; [3]Department of Rheumatology, Salford Royal Hospital, Manchester Academic Health Science Centre, Salford, UK; [4]Centre for Musculoskeletal Research, Faculty of Biology, Medicine and Health, The University of Manchester, UK.

Abstract

Objective

The idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of immune-mediated systemic disorders that commonly target skeletal muscles. The aim of our review is to remind clinicians to be vigilant of common mimickers, and what red flags to look for to avoid misdiagnosis.

Methods

We reviewed the clinical documentation and investigation results of illustrative real-life case examples of significant IIM mimickers with valuable learning points. Following an initial diagnosis of IIM, the patients had been referred to our Adult Neuromuscular Service at Salford Royal Hospital Northern Care Alliance NHS Foundation Trust, UK.

Results

Four cases, two males and two females, were analysed. Retrospective review of key case-specific features suggestive of alternative diagnoses were identified and described, prompting a broader discussion of common disease groups that can mimic IIM.

Conclusion

The presentation of IIM is heterogeneous and the differential diagnosis wide. Several non-inflammatory conditions can present as mimickers of IIM, each requiring a different management approach.

Key words

myositis, muscular diseases, diagnosis

Italo Marago, MD
James B. Lilleker, MRCP, PhD
Hector Chinoy, FRCP, PhD

Please address correspondence to:
Hector Chinoy,
Centre for Musculoskeletal Research,
Manchester Academic
Health Science Centre,
The University of Manchester,
2nd floor, Stopford Building,
Oxford Road,
Manchester M13 9PT, United Kingdom.
E-mail: hector.chinoy@manchester.ac.uk

Orcid ID: 0000-0001-6492-1288

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Introduction

The idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of immune-mediated systemic disorders that commonly target skeletal muscles. A timely and correct diagnosis of IIM is essential for prompt initiation of immunosuppressive treatment to dampen the inflammatory response and prevent irreversible tissue damage, and to provide appropriate patient counselling. However, the presentation of IIM is not stereotypical: extramuscular involvement including cutaneous, respiratory, and cardiovascular manifestations is common; laboratory and electrophysiological results can be variable; histological features such as inflammatory infiltrates can be absent or present to a variable degree within different subtypes of IIM, whilst they can also be found in myositis mimics. The heterogeneity of IIM classification has further increased in the last decades as the term "polymyositis" has been largely replaced in favour of more specific clinic-serological subtypes that offer additional prognostic information (1). The understanding of IIM is constantly expanding (2) and as knowledge is gathered some authors have proposed that IIM is best viewed as a spectrum of disease rather than a single entity (3).

It is therefore not unsurprising that the differential diagnosis of IIM is wide. We have previously described the common pitfalls in the diagnosis of IIM, including common mimickers, and what red flags the clinician must be vigilant for to avoid misdiagnosis (4). The aim of our review is to reinforce these messages using illustrative real-life case examples from the Adult Neuromuscular Service at Salford Royal Hospital, UK.

Case 1

A 62-year-old woman had been complaining of a 10-year history of worsening muscle weakness. She was increasingly struggling when trying to get up from sitting or getting out of cars, and increasingly started to notice difficulties in hand grip and lifting her head from a pillow which brought her to seek medical attention. There was also a history of bilateral calf aching pain, particularly after walking for a few miles, that resolved on resting. There was no sudden decline in her symptoms but rather a gradual progressive deterioration over 10 years. Family history was significant for her father having some proximal weakness in his legs, who died in his 70s from vascular dementia. There was no dysphagia, no rash, no history of developmental delay, and she had never been exposed to a statin.

Examination revealed mild neck flexor and facial weakness. Eye movements were normal. Her tongue was slightly slender without fasciculations. Tongue movements were normal. In the limbs there was thinning of the shoulder girdle musculature and to a lesser extent of the volar forearm. There was similar wasting of the anterior thigh muscles with preservation of muscle bulk distally. Power examination revealed weakness in bilateral elbow extension (4-), wrist extension (4+) and wrist flexion (4-), with clear weakness of the long finger flexors. In the lower limbs there was mild hip flexion weakness (4), some wasting of the quadriceps but no weakness, reduced ankle dorsiflexion (4+) with preserved plantarflexion. Reflexes were suppressed symmetrically but plantar responses were downgoing. Sensory examination was unremarkable.

The initial working clinical diagnosis was inclusion body myositis (IBM). A CK level was raised at 1,174 IU/L. Interestingly, an EMG showed myopathic features but with widespread myotonic discharges. An MRI scan of the pelvis and thighs showed selective fatty atrophy of the distal gluteus maximi, paraspinals, and distal quadriceps (especially vastus lateralis) bilaterally. A myositis antibody panel was negative, including anti-HMGCR and anti-CN1A autoantibodies. Screening for Pompe disease, HIV, and hepatitis B/C was negative, while a repeat CK was 472 IU/L. A muscle biopsy of the tibialis anterior showed significant muscle fibre size variation, atrophy and regeneration in the absence of inflammation. There were rimmed vacuoles on trichrome staining suggestive of a vacuolar myopathy. There were no inflammatory infiltrates or upregulation of MHC class I. In the face of the increasing evidence

against IBM (lack of typical pattern of weakness in lower limbs, prominent myotonia on EMG, and lack of inflammatory features on muscle biopsy), the diagnosis was reconsidered, with a late onset genetic myopathy felt more likely. Given the prominent pain and myotonic features on EMG, genetic testing for myotonic dystrophy type 2 (proximal myotonic myopathy) was performed. This showed a pathogenic expansion CCTG repeat in the CNBP gene, confirming the diagnosis.

The final diagnosis was myotonic dystrophy type 2.

Genetic myopathies

Genetic myopathies are an important differential diagnosis in IIM. The case above illustrates a case of myotonic dystrophy type 2 presenting with a chronic indolent progressive course of predominantly distal muscle weakness that resembled the clinical appearance of inclusion body myositis. Key to the correct diagnosis in this case was an extensive workup at a specialist tertiary centre including a multidisciplinary team (MDT) evaluation with expert neuromuscular pathologists.

Features that favour a genetic myopathy are dependent on the underlying specific diagnosis. Age of presentation can vary from childhood, such as in Duchenne muscular dystrophy, to adult onset, *e.g.* Becker muscular dystrophy, or even after the 5th or 6th decade of life, *e.g.* several limb-girdle-muscular-dystrophy (LGMD) subtypes. We have recently described a case series of adult-onset LGMD type R12 (ANO5-related) patients that were treated as IIM for several years (5). Common to both conditions are a presentation with proximal limb weakness, hyperCK-aemia and some histological features mimicking IIM. Other limb girdle muscular dystrophies may also mimic IIM, particularly dysferlinopathies (6), facioscapulohumeral muscular dystrophy, myotonic dystrophy, myofibrillar myopathies, dystrophinopathies, and hereditary inclusion body myopathies.

Importantly, there is usually a coexistence of inflammation and prominent fatty atrophy in genetic myopathies at presentation. Observing significant fatty replacement of muscle on T1 weighted muscle MR imaging at presentation should raise suspicion about an IIM diagnosis. Such patterns of selective muscle groups involvement can be evident on MRI imaging and biopsy, and are rather different from the patchy inflammation found in IIM (7). Finally, myotonia as seen clinically and/or on EMG can point to myotonic dystrophy, albeit one must be mindful that myotonia can be found in other muscle diseases (8, 9).

A special consideration needs to be mentioned on the inheritance of genetic myopathies. Whilst a genetic aetiology may occasionally be suggested by a positive family history, absence thereof must not lower the clinician's suspicion. It is not uncommon for these conditions to be transmitted in a recessive pattern, at times with reduced penetrance or even secondary to sporadic mutations. Similarly, genetic myopathies may present late in life and may go unrecognised or undiagnosed in close relatives. In this case, cascade testing of other family members is ongoing.

Finally, some genetic myopathy presentations may lack obvious red-flags, especially at an early stage, and treatment with immuno-suppressive regimens including steroids has been observed in several cohorts (5, 6). An initial chemical response in CK can be observed and may be falsely reassuring of an IIM diagnosis, but a clear objective clinical response in muscle strength is not routinely observed.

Table I highlights the key differences between genetic myopathies and inflammatory myositis.

Case 2

A 31-year-old man was referred to the specialist neuromuscular rheumatology clinic for recurring cramps and myalgia. He had first noticed his symptoms when standing up all day at a festival. The symptoms persisted for months and affected his right leg and his upper limbs, with muscles being tender to palpation. His symptoms were exacerbated within a few minutes of starting any form of exercise including walking. He had been started on three courses of prednisolone up to 50mg per day for a presumptive diagnosis of polymyositis with little to no relief. The steroids were eventually stopped as side effects ensued.

There was no family history of neuromuscular diseases and his past medical history was only significant for asthma. Physical examination revealed significant pain-limited movement of shoulder and pelvic girdles without any objective weakness.

Serial CKs had been fluctuating widely, presenting at 1,300 IU/L, peaking at 3,000 IU/L, and lowest levels being of around 100 IU/L. An extended myositis antibody panel was negative. Muscle PYGM mutations were negative for McArdle disease. Blood screening test for Pompe disease was negative. An EMG showed no evidence of myotonic discharges or myopathic process. Acyl-carnitine profile was abnormal with moderately increased medium chain acyl carnitines in a pattern suggestive of myoadenylate deaminase. This prompted the suspicion of multiple acyl-coA dehydrogenase deficiency (*i.e.* glutaric acidemia type 2, MADD). Genetic testing confirmed a mutation in the EFTFDH gene. The patient was counselled about his MADD diagnosis and commenced on riboflavin which helped his symptoms.

The final diagnosis was multiple acyl-coA dehydrogenase deficiency (MADD).

Metabolic myopathies

Metabolic myopathies, including MADD as in the case above, can present in adulthood with features that overlap IIM. We have discussed in detail a practical approach to this category of disorders elsewhere (10), however we will highlight here certain key features that may hint towards the diagnosis of a metabolic myopathy.

Myalgia and fatigue, rather than weakness, are usually more pronounced in patients with metabolic myopathies. The symptoms are typically triggered by certain events (*i.e.* exercise) and are mild or completely absent in between events. CK levels follow a similar pattern of high peaks and low or even normal levels, as is seen in the case above. In particular, CK levels can be

Table I. Summary of different features of genetic myopathies and inflammatory myopathies (IIM).

	Genetic myopathies	IIM
Clinical presentation	Variable. Can range from asymptomatic hyper-CK-aemia to severe proximal and/or distal muscle weakness. Can present with rhabdomyolysis. Family history may be significant for myopathic symptoms.	Usually proximal muscle weakness and connective tissue disease features.
Myositis autoantibodies	Absent.	Usually present.
Serum total CK levels	Variable. Can be very high (*e.g.* >10.000 IU/L). Occasionally normal (*e.g.* congenital myopathy).	Variable. Unusual to be >10.000 IU/L and may be normal in those with paucimyopathic disease.
EMG pattern	Chronic myopathic change. Some conditions have prominent myotonic discharges.	Increased membrane irritability: fibrillation potentials, positive sharp waves, small polyphasic potentials.
Muscle MRI	Severe involvement of selected muscle groups with sparing of neighbouring muscles. Significant fatty infiltration and muscle atrophy at presentation.	Prominent myoedema affecting contiguous proximal muscle groups.
Response to immunosuppression	Non-responsive. A temporary decrease in CK can be observed.	Usually good clinical response and reduction in CK level.

Reproduced from "Limb girdle muscular dystrophy R12 (LGMD 2L, anoctaminopathy) mimicking idiopathic inflammatory myopathy: key points to prevent misdiagnosis. doi: 10.1093/rheumatology/keab553".

in excess of 100,000 IU/L and result in rhabdomyolysis and myoglobinuria that is recurrent. By contrast, rhabdomyolysis is a rare occurrence in IIM, and recurrence even rarer.

Patients with some metabolic myopathies can exhibit the so-called "second wind phenomenon", that is an initial exercise intolerance and symptom occurrence at the beginning of exercise that ameliorates over time, typically after around 10 minutes. This is a reflection of alternative metabolic pathways being activated within the same exercise session, and is most typical of glycogen metabolic diseases such as McArdle. Another hallmark of McArdle disease is the painful muscle contracture which can occur in exercised muscles and can cause rhabdomyolysis.

Other clues to metabolic myopathies (including mitochondrial disease) can be the finding of systemic features, such as short stature, lipomas, learning difficulties, epilepsy, diabetes, hepatic involvement, ophthalmoplegia, and retinopathy. Finally, a maternal inheritance, when and if this is present, can be further indicative of a mitochondrial disease.

Case 3.

A 79-year-old man had presented to his GP with a 2 -year history of worsening bilateral calf pain, worse at night, present on sitting and relieved by walking. On examination there was no muscle wasting or fasciculations, tone and muscle power were normal. Lower limb deep tendon reflexes were attenuated and sensory examination to vibration was reduced to the hips bilaterally. CK was elevated at 308 IU/L and 799 IU/L on two separate occasions. A muscle MRI was organised that showed a feathery pattern of high signal consistent with myoedema in the bilateral gastrocnemii with some fatty atrophy - this was originally reported as polymyositis at a local hospital. He was then referred to the tertiary neuromuscular centre for further investigations.

The MRI images were reviewed and discussed with musculoskeletal radiologists, with an MDT decision that there was a high suspicion for a diagnosis other than IIM. Nerve conduction studies were organised and these highlighted features of a sensory-motor axonal peripheral neuropathy with a co-existing lumbosacral radiculopathy. EMG confirmed significant asymmetrical denervation and reinnervation suggesting neurogenic changes. An MRI spine showed degenerative spondylolisthesis and disk herniation at multiple levels. A diagnosis of co-existing peripheral neuropathy with radiculopathy was made, and the patient was referred onward to neurology.

The final diagnosis was co-existing peripheral neuropathy and radiculopathy.

Neurological disease

Neurological disease can occasionally be mistaken for IIM. The case above is an example of the coexistence of two common neurological problems in the same patient, peripheral neuropathy and lumbo-sacral radiculopathy, that contribute to an unusual pattern of significant myalgia and mild CK rise. In retrospect, the significant degenerative disease of the lumbosacral spine and bilateral asymmetrical radiculopathy were the underlying cause of the symptoms and raised CK. A key learning point from this case is the initial diagnosis of polymyositis made because of myoedema on muscle imaging. This is a useful reminder that the diagnosis of IIM is best achieved after review of clinical, laboratory, immunological and neurophysiological studies, in addition to imaging and biopsy when these are pursued. Myoedema alone on muscle MRI is not specific to IIM and can represent secondary inflammatory change from other aetiologies, including muscle denervation. Interestingly, denervation can also cause pseudo-inflammatory change on muscle biopsy, further adding to the complexity.

Other neurological diseases can have symptoms that overlap IIM and have a potential for misdiagnosis. Kennedy's disease (Spinobulbar muscular atrophy) is an X-linked genetic disorder presenting with appendicular weak-

ness, atrophy, and hyperCKaemia. However, contrary to IIM, Kennedy's disease is often characterised by bulbar involvement (typically perioral fasciculations) and endocrine features. Symptom onset is usually in adult males between the third and fifth decade of life. Family history can be uninformative given the X-linked transmission pattern. Diagnosis can be confirmed via genetic identification of CAG trinucleotide repeat expansion in the androgen receptor gene.

Motor-predominant neuropathies, usually of an autoimmune/inflammatory or paraneoplastic aetiology, can present with weakness and cramping. The detailed intricacies of such conditions are beyond the scope of this paper, however keys to accurate diagnosis here relies on the adoption of a multidisciplinary approach with early involvement of neurologists, neurophysiologists, and potentially oncologists.

In general, we have found that neurologic diseases are accompanied by moderate CK elevations only, and rarely go above around 1,000 IU/L.

Case 4

A 44-year-old woman had been referred to the tertiary neuromuscular centre for review of her 2-year history of muscle fatigue, struggling with daily tasks such as going up the stairs and lifting her arms. The symptoms had followed a period of feeling generally unwell and depression that was secondary to Hashimoto's disease (at diagnosis TSH was 146 μIU/mL and anti-TPO antibodies were positive). Her symptoms persisted despite commencement on thyroid hormone replacement therapy. On examination there was no evidence of proximal or distal muscle weakness, no rash or nailfold changes, no synovitis. There was some tenderness on palpation bilaterally at the insertion of the adductor longus, anterior chest wall and the trapezii.

An initial myositis autoantibody panel was weakly positive for anti-Mi2 autoantibodies. An MRI thighs showed myoedema in the bilateral adductor longus. In response to these findings, she had been commenced on MMF for 6 weeks for a presumptive diagnosis of IIM, then switched to azathioprine as became intolerant and referred to the neuromuscular centre for a second opinion.

A repeat myositis panel using the EUROLINE Inflammatory Myopathies 16 Ag (IgG) commercial line blot immunoassays (LIA) (Euroimmun, Lubeck, Germany) proved to be negative for anti-Mi2 autoantibodies, suggesting the initial result was likely a false positive. A review of MRI images with neuromuscular radiologists did confirm isolated oedema of the adductor longus bilaterally which was unusual for myositis and more likely related to chronic muscle strain (*e.g.* due to exercise), or residual changes related to muscle oedema secondary to hypothyroidism. A diagnosis of hypothyroid myopathy was made, azathioprine stopped and the patient reassured.

The final diagnosis was hypothyroidism masquerading as IIM.

Acquired non-inflammatory myopathies

Myalgia and/or weakness, possibly with a raised CK, can be found in a plethora of other acquired disorders that do not solely or even primarily affect the muscle. It is the example of the case above where the remnants of muscle fatigability from hypothyroidism have persisted for years despite treatment of the underlying aetiology. In addition, this case highlights a concept we have explored elsewhere of the false positivity of autoantibodies in myositis and the importance of not associating an isolated positivity as synonymous with a diagnosis of IIM (11).

Endocrine disorders such as hypo- or hyperthyroidism, Cushing's syndrome, acromegaly, and hyperparathyroidism can all present with myalgia and/or muscle fatigue with hyperCKaemia. Each of these conditions can alter muscle cell homeostasis at different levels of the cellular metabolism and result in cellular dysfunction (12). The myopathy can be as frequent as 80% of cases in hypothyroidism in some series(13) and cases of necrotising myopathy have also been described (14). An informative review on the topic has been discussed by Fariduddin *et al*. (15).

Deficit or excess of virtually any electrolyte disturbance, most importantly sodium, potassium, magnesium, calcium, or phosphorus, can cause muscle weakness, fatigue, pain, or cramps by way of disrupting the stability of the sarcolemmal membrane.

Critical illness can result in a myopathy that can be protracted in time (16). This type of myopathy is likely multifactorial, with muscle disuse, malnutrition, use of paralytic agents, sepsis and any of the factors discussed above being potential contributors.

Finally, one must consider the issue of drug-induced myopathies. By far the most widely known phenomenon is that of myalgia following the administration of a statin (3-hydroxy-3-methylglutaryl-CoA reductase inhibitors). This has to be distinguished from a subtype of IIM of immune-mediated-necrotising-myopathy (IMNM), where around 50% of patients have a history of statin use. IMNM is far less common than the direct myotoxic effect of statin use and characteristically has a raised CK, poor prognosis and does not improve following the discontinuation of the statin. Other drugs that can commonly result in myalgia or weakness include glucocorticoids, amiodarone, colchicine, chloroquine, hydroxychloroquine (12, 17), as well as antiretroviral drugs such as zidovudine (18). These are all characterised by gradual onset associated with chronic use of the drug and improvement after discontinuation of the offending agent.

Conclusion

The cases above are real-life examples of the importance of appropriate diagnosis in IIM and its many potential mimics. Several factors can contribute to this phenomenon. Perhaps one of the more representative is that IIM can present variably, and no "one size fits all" is available for IIM in terms of age of presentation, gender, natural course of the disease progression, and response to treatment. IIM is also more common than the majority of its mimics, perhaps leading clinicians to think more easily of an atypical presentation of IIM rather than reconsider the initial diagnosis. Similarly, it is not uncommon for IIM to be resistant to treatment, and second

Table II. Red flags for alternative diagnoses in patient with apparent inflammatory myopathy.

Red flag	**Key alternative diagnoses to consider**
Positive family history for myopathic symptoms	Genetic myopathies, neuropathies or metabolic myopathies
Asymmetric and distal weakness (except sporadic IBM)	Genetic myopathies (*e.g.* Fascioscapulohumeral muscular dystrophy, myotonic dystrophy and hereditary forms of IBM)
Muscle hypertrophy	Genetic myopathies (*e.g.* caveolinopathy, sarcoglycanopathy). Manifesting carriers of dystrophinopathies
Early muscle atrophy	Genetic myopathies (many), neurological disease (*e.g.* Amyotrophic lateral sclerosis), metabolic myopathy (*e.g.* Pompe disease)
Fasciculation or cramping	Neurological disease (*e.g.* amyotrophic lateral sclerosis or peripheral nerve hyperexcitability) or metabolic abnormality (*e.g.* Hypocalcaemia)
Enzymes> 100 x normal upper limit	Metabolic myopathies (*e.g.* Mcardle's disease, carnitine palmitoyltransferase ii deficiency)
Treatment with myotoxic drug	Drug induced myopathy
No non-muscle symptoms	Pure myopathy syndromes have wide differential. Genetic myopathies should be considered
No response to therapy (except sporadic IBM)	Genetic myopathies, neuropathies or metabolic myopathies
No abnormal gammaglobulins or autoantibodies	Genetic myopathies, neuropathies or metabolic myopathies
Muscle magnetic resonance imaging demonstrating severe selective fatty replacement of individual muscles	Genetic myopathies, neurological disease (*e.g.* Spinal disease/ radiculopathy)
Muscle magnetic resonance imaging normal or demonstrating atrophy only	Metabolic myopathies, sarcopenia of aging
Rhabdomyolysis, especially if recurrent	Metabolic myopathies

Adapted from "Pitfalls in the diagnosis of myositis", https://doi.org/10.1016/j.berh.2020.101486

or third line immunosuppressive regimen are routinely employed (19), leading to further diagnostic delays of IIM mimics.

The potential negative effects of misdiagnosis are twofold: 1) IIM treatment with potent immunosuppression can lead to unnecessary side effects including potentially life-threatening infections; 2) appropriate management of IIM mimics is delayed, which is particularly worrisome in some IIM mimics for which disease modifying therapies are now available (*e.g.* Pompe disease). Of note two out of four of the cases described above had received immunosuppressive agents. Vice versa, it is also true that patients with IIM should receive an accurate and prompt diagnosis. Whilst a discussion on IIM and its subtypes is beyond the scope of this manuscript and can be found elsewhere (20), it is worth mentioning that certain IIM subtypes such as anti-TIF1-γ positive myositis have a high incidence of associated cancer (21). The myositis symptoms can often precede the cancer diagnosis, and therefore great care must be exercised in actively screening for cancer in these patients. The factors above have contributed to old classifications for IIM such as "polymyositis" and "dermatomyositis" as per the original Bohan and Peter criteria (22), to be progressively replaced with more specific clinic-serological subtypes (1) that are likely to evolve even more in the near future (23). An overarching principle that has emerged from the cases above is the importance of a holistic approach to the diagnosis of IIM rather than relying on isolated investigation findings: case 1 highlights that a family history can be absent in genetic myopathies; in case 2 we described how wide fluctuations in symptoms and CK levels should raise the suspicion for metabolic myopathies; case 3 displays a misdiagnosis of polymyositis on the account of myoedematous changes on muscle MRI; case 4 reminds us how myositis antibodies, whilst very valuable, do have false positive results (24); Therefore, in the presence of red flags as highlighted in Table II, it is prudent to think more carefully about myositis mimics and not to hesitate reconsidering the diagnosis. Great advances have been made in the field of myology in the past few decades, so much so that the diagnostic journey of most patients can lead to a precise diagnostic entity that influences specific management and counselling. Even in the absence of specific treatment options for some nosological entities, muscle exercise can still prove beneficial in providing an objectively measurable improvement in muscle function (25).

Finally, the need for a multidisciplinary approach to the myopathic patient cannot be over-emphasised. Early referral to specialist tertiary myositis centres is advised in difficult cases, where additional facilities, including access to neuromuscular MDT meetings with specialist physicians, pathologists and radiologists, can occur early and facilitate prompt diagnosis.

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