Review

The atypical manifestations in adult-onset Still's disease, beyond the classical clinical triad at the intersection of environment and genetic background

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ABSTRACT

Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder traditionally characterised by the typical clinical triad of high spiking quotidian fever, evanescent rash and inflammatory arthritis. However, growing evidence suggests that AOSD encompasses a much broader clinical spectrum, including a variety of rare and atypical manifestations. This review aims to provide a comprehensive overview of these unusual clinical features in AOSD. Importantly, many of these clinical characteristics may mimic infectious, malignant, or autoimmune disorders, contributing to diagnostic delay and therapeutic challenges. An increased awareness of these uncommon presentations may facilitate earlier diagnosis, improve clinical management, and contribute to a more comprehensive understanding of this complex multisystem autoinflammatory disorder. In addition, the possible contributing role of environment and possible different genetic background is discussed in contributing to the heterogeneity of patient clinical picture.

Introduction

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder at the crossroad of autoinflammation and autoimmunity (1). Pathogenetically, both arms of the immune system contribute to the deregulated inflammatory underlying response, converging on IL-1 signalling pathway and leading to the disease development and patient manifestations (2). AOSD is usually characterised by classical clinical triad of high-spiking quotidian fever, evanescent salmon-pink rash, and inflammatory joint involvement, both arthritis or arthralgia (3). Additional manifestations include a various degree of multi-organ involvement like lymphadenopathy and hepatosplenomegaly (4). In addition, life-threatening complications, including macrophage activation syndrome (MAS) and parenchymal lung disease, may burden the clinical course of these patients. AOSD is also characterised by a typical hyperferritinemia and increases of laboratory markers (5-7). Historically, independently from initial clinical features, monophasic, recurrent and persistent disease courses are recognised in AOSD (8). Although the initial clinical picture can be similar in different patients, the developing disease course may be highly heterogeneous (9). Thus, different patient clusters have been recently introduced (10). These are associated with the main clinical manifestations of fever, joint involvement and skin rash, but clinical differences enable them to be variously characterised as 'juvenile or transitional', 'uncomplicated', 'hyperferritinaemic' and 'catastrophic' (10). The clinical heterogeneity may be further increased due to possible uncommon manifestations involving skin, lungs, heart, nervous system, kidneys, eyes and haematological compartment (11). These manifestations may occur during the disease course or, in some patients, represent the initial clinical presentation, preceding the development of the classical typical triad and making challenging the diagnosis. Importantly, some of these uncommon manifestations, are associated with significant morbidity and mortality and may require prompt recognition and

treatment (12, 13). The latter could be consequently postponed due to these uncommon disease manifestations, which may significantly delay the administration immunosuppressive therapies. Glucocorticoids, conventional synthetic- and biologic DMARDs are variously administered to manage patients with AOSD (14-16). However, the evidence about the occurrence of rare manifestations in AOSD is mainly based on case reports and small case series, thus, challenging the patient management. On these bases, given the fragmented nature of the available evidence, we aimed to review the rare and atypical manifestations of AOSD, discussing their clinical characteristics, diagnostic challenges, and possible therapeutic considerations.

Methods

We designed a comprehensive search of literature on AOSD following proposed guidelines for preparing biomedical narrative review (17). MedLine (*via* PubMed) was assessed as well as the bibliography of relevant articles was also hand-searched for identification of other potentially suitable studies. For the purposes of this review, rare manifestations were defined as clinical features attributable to AOSD which are not included among the classical diagnostic hallmarks of the disease and reported with a frequency lower than 5% in available large international cohorts (18-21). This definition was adopted to distinguish uncommon organ involvement from the more frequently recognized manifestations of AOSD. Given the rarity of these clinical features, case reports and small case series were considered as additional sources of information.

Skin manifestations

The skin involvement is one of the most typical clinical signs of AOSD manifesting with evanescent salmon-pink rash on arms and trunk paralleling with high spiking fever (22). However, an expanding body of evidence has increasingly described a wide spectrum of atypical dermatological features, significantly complicating the diagnostic process of patients with AOSD (22). Among the uncommon skin presentations, persistent pruritic eruptions represent the most frequently reported manifestation (22). Unlike the transient and non-pruritic classical rash, these lesions are characterized by persistent papules, plaques, or linear erythematous lesions associated with intense pruritus (23-27). The histopathological examination may frequently show dyskeratotic keratinocytes within the upper epidermis and superficial dermal inflammatory infiltrates (28). In addition, urticarial lesions, persistent flagellate erythema, dermatomyositis-like eruptions, prurigo pigmentosa-like lesions, vesiculopustular eruptions, erythema multiforme-like lesions, psoriasiform eruptions, and lupus erythematosus-like facial erythema have been associated with AOSD (22, 29-34). Angioedema, facial oedema, calcinosis cutis, erythema nodosum, oral mucosal lesions, and cellulitis-like eruptions have also been described rarely described in AOSD (22, 35-41). In some cases, although uncommon, these skin features may precede systemic manifestations and occasionally represent the initial clinical feature of AOSD. Thus, the recognition of these non-classical skin manifestations is of clinical importance because they may also mimic infectious, autoimmune, allergic, or neoplastic disorders, resulting in diagnostic delay (22). In addition, some experiences have suggested an association between persistent skin lesions, beyond 24 hours, and increased systemic disease activity, raising the possibility that these may identify a subset of patients with a more severe clinical phenotype (35, 41). The persistent lesions have been associated with occurrence of MAS and parenchymal lung disease highlighting the clinical relevance in patients with AOSD (22). Therapeutically, no specific indication emerged from available literature.

Interestingly, most atypical cutaneous manifestations have been reported in Asian populations, suggesting that geographical distribution, together with genetic susceptibility and environmental factors, may contribute to shaping the dermatological clinical phenotype of AOSD.

Cardiac manifestations

Cardiac involvement represents one of the most clinically significant atypical manifestations of AOSD, associated severe morbidity and mortality (42). Consequently, clinicians should maintain a high index of suspicion for cardiac manifestations in patients presenting with unexplained cardiac symptoms in the setting of systemic inflammation and suspected AOSD. Cardiac manifestations in AOSD may affect all the layers of the heart, including pericarditis, which is the most common retrieved feature, endocarditis and/or myocarditis. The latter emerged as the most frequently reported condition in literature (43). Clinical presentation ranges from mild myocardial inflammation to fulminant myocarditis, with patients presenting with chest pain, dyspnoea, arrhythmias, cardiogenic shock, or acute heart failure (43-46). The diagnosis is often supported by elevated cardiac biomarkers, electrocardiographic abnormalities, echocardiographic findings, and, increasingly, cardiac magnetic resonance imaging, which has become a valuable tool for the detection of myocardial inflammation and oedema. Recently, predictive factors for myocarditis were reported, including skin rash and increased values of systemic score (22). In addition, myocarditis has been associated with MAS, in the context of patient life-threatening evolution (47, 48). Furthermore, the cardiac tamponade represented another rare cardiac manifestation in AOSD (49, 50). Although pericardial effusion is not uncommon in AOSD, progression to hemodynamically significant tamponade remains rare and may require urgent pericardiocentesis. In some reported cases, cardiac tamponade constituted the presenting manifestation of the disease, further highlighting the diagnostic complexity of atypical AOSD presentations (49, 50). Additional uncommon manifestations included infective endocarditis-like presentations, cardiac valve involvement, complete atrioventricular block, and acute heart failure. These manifestations may mimic infectious, ischaemic, or primary cardiac disorders, potentially delaying recog-

nition of the underlying inflammatory disease (43, 51-54). The early recognition of cardiac involvement is essential, as prompt initiation of high-dose glucocorticoids and targeted biologic therapies may lead to rapid clinical improvement and prevent irreversible cardiac damage (3, 49).

The majority of reported cardiac manifestations originate from Caucasian populations, although reporting bias cannot be excluded.

Neurological manifestations

Neurological involvement in AOSD is uncommon but may represent one of the most challenging and potentially severe manifestations of the disease, especially in the context of complications (20). Central and peripheral nervous system features have been increasingly reported. Amongst them, aseptic meningitis was the most frequently reported condition (20, 55-57). Patients usually present with headache, fever, neck stiffness, photophobia, and cerebrospinal fluid pleocytosis in the absence of an identifiable infectious agent. Although the clinical presentation may closely resemble bacterial or viral meningitis, extensive microbiological investigations are generally negative, and symptoms often improve following immunosuppressive treatment. The close collaboration between rheumatologists and neurologists is needed to carefully manage these patients. In addition, neutrophilic meningitis represents a particularly distinctive manifestation of AOSD (55, 58). Characterised by marked neutrophilic predominance in the cerebrospinal fluid, this condition may reflect the intense innate immune activation underpinning AOSD but highlighting significant diagnostic challenges due to its resemblance to infectious meningitis (55-58).

In addition, encephalitis and meningoencephalitis have also been described, occasionally presenting with altered mental status, seizures, cognitive dysfunction, or focal neurological deficits (59, 60). In some cases, neuroimaging findings suggest diffuse inflammatory involvement of the central nervous system, while cerebrospinal fluid analysis may reveal inflammatory changes of varying severity. However, no distinctive radiologic features have been described in complicating. Other rare cerebrovascular manifestations have also been reported, including acute ischemic stroke and disseminated cerebral thrombotic microangiopathy reflecting endothelial dysfunction and systemic hyperinflammation (61, 62). Another neurological complication is posterior reversible encephalopathy syndrome (PRES), a condition characterised by headache, seizures, visual disturbances, altered consciousness and characteristic reversible vasogenic oedema on magnetic resonance imaging. Although uncommon, PRES should be considered in patients with AOSD who develop acute neurological symptoms, particularly in the setting of severe systemic inflammation or immunosuppressive therapy (63).

Peripheral nervous system involvement is considerably less common and includes peripheral neuropathy and cranial nerve palsies (57).

Importantly, most neurological manifestations appear to respond favourably to prompt immunosuppressive treatment, emphasising the importance of early recognition and accurate differential diagnosis (20).

Taken together, these observations suggest that neurological manifestations have been reported predominantly in Asian populations, supporting the possible role of ethnicity in this context.

Pulmonary manifestations

Parenchymal lung involvement in AOSD is increasingly recognized as a potentially severe and life-threatening complication since associated with MAS (64, 65). Although initially subtle, parenchymal lung involvement manifests with dyspnoea, tachypnoea and cough. Unlike adults, affected children and adolescents can be characterised by clinical features including acute erythematous clubbing, atypical rash and anaphylaxis-type reactions to tocilizumab (66-68). The occurrence of lung involvement in AOSD has corresponded with the increasing use of inhibitors of IL-1 and IL-6, and many individuals with this manifestation have a history of exposure to these drugs (69, 70). Histologically, this manifestation seems to be related with features of pulmonary alveolar proteinosis and/or lipoid pneumonia (71). It is still unclear if this complication may evolve with interstitial lung disease or not over time.

In addition to this life-threatening evolution, despite mild pleural effusion may frequently occur as part of disease flare, a broad spectrum of atypical pulmonary manifestations has been also reported, ranging from transient inflammatory infiltrates to acute severe respiratory failure in the context of acute respiratory distress syndrome (ARDS). Among the other pulmonary manifestations reported in the available literature, pneumonia-like presentations were reported. These cases often present with fever, cough, dyspnoea and radiographic pulmonary infiltrates, closely mimicking infectious pneumonia. However, microbiological investigations resulted to be negative, and patients benefit to immunosuppressive rather than antimicrobial therapy. Acute respiratory failure represents one of the most severe pulmonary complications of AOSD and may occur either as an isolated manifestation or in association with macrophage activation syndrome. Similarly, ARDS has been described in many cases and is associated with significant morbidity and mortality (72, 73). Additional rare pulmonary manifestations include diffuse pulmonary nodules, pulmonary arterial hypertension, lobar atelectasis, and bilateral pleural effusions (74-77). Finally, pulmonary arterial hypertension has been recently reported in patients with AOSD characterised by MAS, eosinophilia and HLA-DRB1*15 allele (78).

Taking together all these observations, given the potentially fulminant course of some pulmonary manifestations, clinicians should maintain a high degree of suspicion when patients with AOSD develop unexplained respiratory symptoms. Early recognition and prompt initiation of immunosuppressive therapy may be crucial for improving clinical outcomes and preventing irreversible pulmonary damage.

Taken together, these observations in-

dicate that atypical pulmonary manifestations have been described predominantly in Caucasian patients.

Gastrointestinal and liver manifestations

Gastrointestinal and liver involvements in AOSD are generally underrecognised by the more characteristic clinical manifestations of the disease. However, a variety of uncommon gastrointestinal and hepatobiliary presentations have been reported, some of which may constitute the initial manifestation of AOSD or complicate its clinical course (79). Liver involvement is relatively common in AOSD and usually manifests as mild-to-moderate elevations of serum transaminases, which are associated with a careful evaluation of the administration of some drugs such as methotrexate. However, severe hepatic injury represents an uncommon but clinically significant manifestation (79). Reported cases have described marked hepatocellular damage, acute hepatitis, and, in rare instances, progression to acute liver failure, often in the context of MAS (80-83). In this context, autoimmune hepatitis-like presentations have also been described (84). These cases may point put considerable diagnostic challenges because of overlapping clinical, laboratory, and histopathological findings. Distinguishing between primary autoimmune liver disease and AOSD-related hepatic involvement is essential, as management strategies and prognostic implications may differ substantially. In addition, among the gastrointestinal manifestations, intestinal pseudo-obstruction represents one of the most unusual presentations (85). Patients may develop abdominal pain, distension, nausea, vomiting, and impaired intestinal motility in the absence of a mechanical obstruction (85). Additional rare gastrointestinal manifestations include peritonitis and inflammatory involvement of the small intestine, such as duodenojejunal inflammation associated with chronic vomiting (85). These conditions may mimic infectious, surgical, or inflammatory bowel disorders, frequently leading to extensive diagnostic investigations before the underlying diagnosis of AOSD is established.

Given the nonspecific nature of many gastrointestinal symptoms, clinicians should consider AOSD in the differential diagnosis of patients presenting with unexplained systemic inflammation and atypical hepatobiliary or gastrointestinal manifestations. Early recognition may prevent unnecessary invasive procedures and facilitate the timely initiation of appropriate immunosuppressive therapy.

Taken together, these observations suggest that atypical gastrointestinal and hepatic manifestations have been reported predominantly in Asian populations.

Renal manifestations

Renal involvement in AOSD is uncommon and is generally considered an atypical manifestation of the disease. Unlike other systemic inflammatory disorders, the kidneys are infrequently affected in AOSD; however, a broad spectrum of renal abnormalities has been described, ranging from acute kidney injury to distinct forms of glomerular disease (86).

Acute kidney injury and many uncommon glomerular pathologies have been reported in association with AOSD. Collapsing glomerulopathy is among the most distinctive and severe renal manifestations, characterised by collapse of the glomerular capillary tuft and podocyte proliferation (87-90). Patients typically present with nephrotic-range proteinuria and rapidly progressive renal dysfunction (87, 89). Other reported glomerular lesions include membranous glomerulonephritis, mesangioproliferative immune complex-mediated glomerulonephritis, and necrotising crescentic IgA glomerulonephritis (91, 92). These findings highlight the remarkable heterogeneity of renal involvement in AOSD and suggest that multiple pathogenic pathways may contribute to kidney injury.

Systemic AA amyloidosis represents another important renal complication, although infrequent due to chronic uncontrolled inflammation which may promote amyloid deposition, leading to progressive proteinuria, nephrotic syndrome and ultimately chronic kidney disease (93).

In consideration of the heterogeneity of these rare renal manifestations, kidney involvement should be considered in patients with AOSD presenting with unexplained proteinuria, haematuria, nephrotic syndrome, or acute deterioration of renal function. In selected cases, renal biopsy may be essential for establishing the diagnosis, guiding treatment decisions, and assessing prognosis.

Unlike other organ manifestations, no consistent geographical predominance has emerged for renal involvement, probably reflecting the extremely limited number of reported cases.

Haematological and thrombotic manifestations

Haematological abnormalities are common in AOSD typically including leucocytosis, neutrophilia, anaemia of chronic inflammation, and thrombocytosis. However, a number of rare haematological and thrombotic manifestations have been reported (94-97).

Among the most severe haematological complications, thrombotic thrombocytopenic purpura (TTP) is recognised, a life-threatening thrombotic microangiopathy characterised by thrombocytopenia, microangiopathic haemolytic anaemia, neurological abnormalities, renal dysfunction and fever. Although rare in AOSD, TTP represents a medical emergency requiring prompt recognition and treatment. Thrombotic microangiopathy (TMA) has also been described in association with AOSD. Similar to TTP, TMA may present with thrombocytopenia, haemolytic anaemia, and organ dysfunction, particularly involving the kidneys and central nervous system. In some cases, cerebral thrombotic microangiopathy has been reported, highlighting the potential for widespread vascular injury in severe inflammatory states. Additional uncommon haematological manifestations may include pure red cell aplasia and acquired amegakaryocytic thrombocytopenia (98-101). These disorders are believed to result from immune-mediated suppression of hematopoietic progenitor cells and may present with

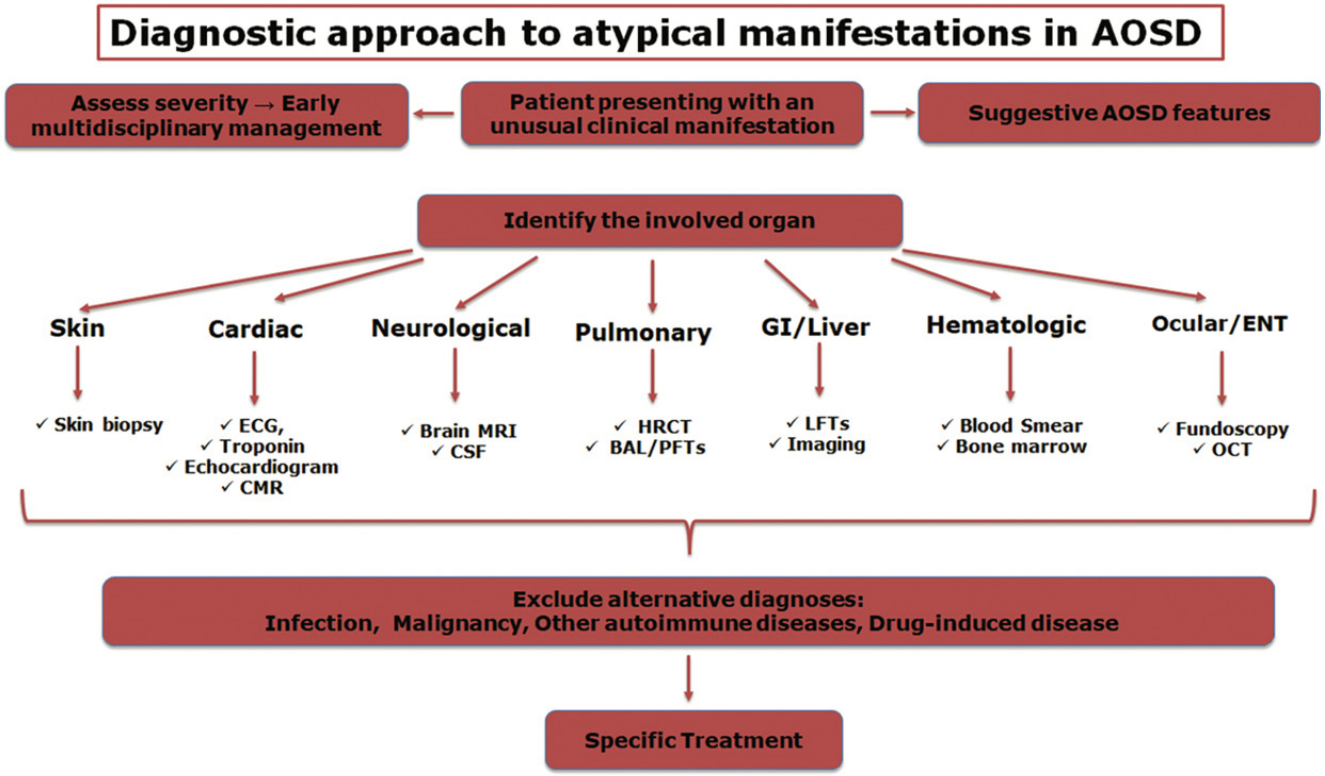


Fig. 1. Diagnostic approach to atypical manifestations in adult-onset Still's disease (AOSD).
Patients presenting with an unusual clinical manifestation should undergo a systematic evaluation according to the involved organ system, including skin, cardiac, neurological, pulmonary, gastrointestinal/hepatic, haematologic and ocular/otorhinolaryngological involvement. Organ-specific investigations may include skin biopsy, electrocardiography (ECG), cardiac biomarkers, echocardiography, cardiac magnetic resonance (CMR), brain magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis, high-resolution computed tomography (HRCT), bronchoalveolar lavage (BAL), pulmonary function tests (PFTs), liver function tests (LFTs), imaging studies, peripheral blood smear, bone marrow examination, fundoscopy, and optical coherence tomography (OCT). Alternative diagnoses, including infections, malignancies, other autoimmune diseases, and drug-induced conditions, should be carefully excluded. The identification of clinical and laboratory features suggestive of AOSD should prompt assessment of disease severity, early multidisciplinary management, and timely initiation of appropriate targeted therapy.

severe anaemia or thrombocytopenia requiring intensive supportive care and immunosuppressive treatment.

Venous thrombotic events have also been reported in patients with AOSD. Persistent systemic inflammation may promote a prothrombotic state through endothelial activation, platelet dysfunction, cytokine-mediated coagulation abnormalities, and increased expression of procoagulant factors. Although venous thrombosis remains uncommon, clinicians should be aware of its potential occurrence, particularly in patients with severe systemic disease activity (102, 103).

Rare haematological manifestations should be considered in patients with AOSD who develop unexplained cytopenias, haemolytic anaemia, thrombocytopenia, or thrombotic events. Early diagnosis and timely initiation of appropriate immunosuppressive and supportive therapies are essential to improve prognosis and reduce disease-related mortality. Conversely, most reported haematological complications have been described in Caucasian patients. Although these observations should be interpreted cautiously, they further support the hypothesis of geographical heterogeneity in the clinical expression of AOSD.

Ocular and otorhinolaryngological manifestations

Ocular and otorhinolaryngological manifestations are among the rarest clinical presentations of AOSD. Although uncommon, these manifestations may result in significant morbidity and occasionally represent the initial clue to the underlying systemic inflammatory disorder.

Among the ocular manifestations reported in the literature, Purtscher-like retinopathy appears to be the most frequently described (104-108). This rare retinal microvascular disorder is characterized by sudden visual impairment associated with cotton-wool spots, retinal haemorrhages, and Purtscher flecken on fundoscopic examination.

Other reported ocular manifestations include panuveitis, multifocal central serous chorioretinopathy, and orbital inflammatory lesions (109-111). These conditions may present with visual disturbances, ocular pain, photophobia, or decreased visual acuity. Because of their rarity and nonspecific clinical presentation, establishing a direct association with AOSD may be challenging. A prompt recognition is essential to avoid unnecessary invasive procedures and to ensure timely initiation of immunosuppressive therapy.

Otorhinolaryngological manifestations are even less frequently reported. Cases of dacryoadenitis, trochleitis, and nasal septal perforation have been described, suggesting that inflammatory

Table I. Usual and unusual organ manifestations in AOSD.

Organ system	Usual manifestations	Unusual manifestations	Predominant ethnicity reported	Key references
Skin	Evanescent salmon-pink rash	Persistent pruritic eruption; Urticaria; Flagellate erythema; Dermatomyositis-like eruption; Prurigo pigmentosa-like eruption; Vesiculopustular eruptions; LE-like facial erythema; Erythema nodosum; Oral mucosal lesions; Cellulitis-like eruptions; Erythema multiforme; Psoriasiform eruptions; Pencil sketch-like papules; Melanoderma; Vitiligo; Facial oedema; Angioedema; Calcinosis cutis	Asian	(22, 25, 28)
Cardiac	Pericarditis	Myocarditis; Epicarditis; Endocarditis; Myocardial dysfunction; Cardiac tamponade; Acute heart failure; Complete AV block; Cardiac valve involvement; Cardiac death	Caucasian	(42, 43, 49)
Pulmonary	Pleural effusion; pleuritis	Pulmonary embolism; Acute respiratory failure; Pulmonary arterial hypertension; Lobar atelectasis; Pneumonia; Diffuse pulmonary nodules; Pulmonary alveolar proteinosis; Interstitial lung disease; ARDS	Caucasian	(7, 64, 69, 78)
Neurological	None consistently reported	Aseptic meningitis; Neutrophilic meningitis; Encephalitis; Meningoencephalitis; Peripheral neuropathy; Cranial nerve palsy; Neuropsychiatric manifestations; Autoimmune meningitis; PRES; Acute ischemic stroke; Disseminated cerebral thrombotic microangiopathy; Epilepsy	Asian	(20, 55, 57)
Gastro-hepatic	Hepatosplenomegaly; liver enzyme elevation	Severe liver injury; Autoimmune hepatitis; Intestinal pseudo-obstruction; Peritonitis; Duodenojejunal inflammation	Asian	(79, 80, 85)
Hematologic	Leucocytosis	Pure red cell aplasia; Thrombotic thrombocytopenic purpura; Thrombotic microangiopathy; Acquired amegakaryocytic thrombocytopenia; Venous thrombosis	Caucasian	(94, 97, 102)
Ocular/ENT	None consistently reported	Purtscher-like retinopathy; Orbital inflammatory lesions; Panuveitis; Central serous chorioretinopathy; Trochleitis; Dacryoadenitis; Nasal septal perforation	Asian/American	(104, 109, 112)

processes associated with AOSD may occasionally involve structures of the upper airways and periocular tissues (112-114).

The rarity of ocular and otorhinolaryngological involvement in a rare disease as AOSD strongly limits current knowledge regarding their prevalence, prognosis, and optimal management. Nevertheless, awareness of these unusual presentations is important, as delayed recognition may result in irreversible visual impairment or unnecessary diagnostic procedures. Multidisciplinary collaboration among rheumatologists, ophthalmologists, and otorhinolaryngologists is required to ensure accurate diagnosis and appropriate treatment. Available evidence suggests that ocular and otorhinolaryngological manifestations have been reported mainly in Asian and American populations. However, the very limited number of published cases precludes definitive conclusions regarding their geographical distribution.

Overview of rare and atypical manifestations

Different rare or atypical manifestations of AOSD were reported in the available literature. Most patients presented with a single atypical manifestation, whereas a smaller proportion exhibited two or more concurrent uncommon manifestations, further highlighting the heterogeneous nature of the disease spectrum. Cutaneous involvement represented the most frequently described category, followed by cardiac and neurological manifestations. Notable combinations included neurological manifestations associated with peripheral nervous system involvement, thrombotic microangiopathy associated with acute kidney injury, myocarditis occurring concomitantly with peritonitis and urticaria, and interstitial lung disease associated with dermatomyositis-like skin eruptions. Notably, the identification of rare and atypical manifestations across further emphasizes the extraordinary clinical heterogeneity of AOSD and supports the concept of the disease as a multisystem inflammatory spectrum rather than a single clinical entity (115). This observation reinforces the need for a comprehensive diagnostic approach when evaluating patients with unexplained systemic inflammation and unusual organ involvement (115-117). In Figure 1, a representative diagnostic algorithm is reported to fully assess the patients presenting rare manifestations associated with AOSD.

Genetic and environmental determinants of rare clinical phenotypes in AOSD

The marked heterogeneity of uncommon manifestations in AOSD may suggest that distinct genetic backgrounds and environmental exposures may contribute to the development of specific clinical phenotypes rather than merely influencing disease susceptibility. Several genetic associations support this hypothesis. Early studies identified

Table II. Diagnostic implications of atypical manifestations in AOSD.

Atypical manifestation	Potential diagnostic challenge	Main differential diagnoses	Clinical clues suggesting AOSD	Key references
Interstitial lung disease	May precede classical manifestations	CTD-ILD, infection, vasculitis, drug-induced pneumonitis	Hyperferritinemia, systemic symptoms, MAS features	(7, 65)
Pulmonary arterial hypertension	May dominate presentation	CTD-PAH, idiopathic PAH, CTEPH	History of inflammatory flares and elevated ferritin	(78)
Cardiac manifestations	Mimics infectious/autoimmune myocarditis	Viral myocarditis, SLE, vasculitis, sarcoidosis	Spiking fever, neutrophilia, high ferritin	(42, 43)
Neurological manifestations	Often delay diagnosis	CNS infection, autoimmune encephalitis, MS, vasculitis	Concurrent systemic inflammatory symptoms	(20, 55)
Renal manifestations	Often attributed to other systemic diseases	ANCA vasculitis, lupus nephritis, amyloidosis	Persistent inflammation and hyperferritinemia	(86, 87, 93)
Severe liver involvement	Mimics hepatitis	Viral, toxic, autoimmune hepatitis	Inflammation disproportionate to hepatic injury	(79, 80)
Ocular manifestations	May appear as isolated ophthalmic disease	Behçet, sarcoidosis, IBD-related uveitis	Typical systemic AOSD features	(104, 109)
MAS	May obscure underlying disease	Sepsis, hematologic malignancy	Extreme hyperferritinemia, cytopenias, low ESR	(6, 12)

associations with HLA-Bw35 (118), HLA-DR4 and HLA-DRw6 (119), with the latter being preferentially associated with chronic articular disease and persistent arthritis. Additional associations involving HLA-DRB112, HLA-DRB115 and HLA-DQB106:02 have subsequently been reported (120-122). Furthermore, polymorphisms involving the IL18 promoter region (123) and the macrophage migration inhibitory factor gene (124) have been linked to increased inflammatory responses. Variants in autoinflammatory disease-related genes, including MEFV and TNFRSF1A, further support a genetic overlap with hereditary periodic fever syndromes and may contribute to different disease courses and atypical manifestations (125-127). Particularly relevant to rare organ involvement is the recent identification of HLA-DRB115, which has been associated with severe delayed hypersensitivity reactions to IL-1 and IL-6 inhibitors and with severe pulmonary phenotypes, including Still's disease-associated lung disease and pulmonary arterial hypertension (69, 70, 78). Environmental factors may provide the second hit required for the emergence of these phenotypes. Several infectious agents have been proposed as triggers, including Epstein-Barr virus, cytomegalovirus, parvovirus B19, rubella virus, measles virus, echovirus 7 and coxsackievirus B4, together with bacterial pathogens such as Yersinia enterocolitica, Mycoplasma pneumoniae, Chlamydia pneumoniae, Brucella abortus and Borrelia burgdorferi (118, 122, 128). Although evidence is largely based on case reports and small series, these observations suggest that specific environmental exposures may activate innate immune pathways in genetically predisposed individuals, favouring the development of distinct clinical patterns and uncommon organ involvement. The striking geographical variability of several rare manifestations reviewed herein further supports the concept of disease-specific gene-environment interactions shaping the clinical spectrum of AOSD.

Critical appraisal and uncommon manifestations at the crossroad of environment and genetic background

All these observations further support the concept of AOSD as a highly heterogeneous systemic inflammatory disorder capable of affecting virtually any organ system. The broad spectrum of uncommon manifestations emphasizes the need for heightened clinical awareness, particularly when patients present with unusual inflammatory features that cannot be readily explained by more common infectious, autoimmune, or malignant conditions, since they may further increase the patient disability (129, 130).

Rare manifestations of AOSD can be interpreted within the broader framework of AOSD pathogenesis, in which a complex interplay between genetic susceptibility and environmental triggers results in dysregulated innate immune responses (131, 132, 133, 134). In genetically susceptible individuals, infections and other inflammatory stimuli may activate pattern-recognition receptors and inflammasome pathways, leading to excessive cytokine production (135, 136). Interestingly, the distribution of uncommon manifestations appears to vary across geographic regions, as shown in Table I, suggesting the involvement of region-specific environmental factors. Such observations raise the possibility that different environmental exposures interact with distinct genetic backgrounds, generating partially divergent immunopathological pathways and ultimately shaping disease phenotype. Rather than representing a single homogeneous disease entity, AOSD may encompass multiple biological endotypes characterised by variable activation of cytokine networks, inflammasome signalling, and

Table III. Prognostic and therapeutic implications of atypical manifestations in AOSD.

Organ system	Atypical manifestation	Association with MAS	Prognostic relevance	Therapeutic implications	Key references
Cardiac manifestations	Myocarditis, pericarditis	High	High	Early high-dose glucocorticoids; IL-1/IL-6 blockade	(42, 43, 47)
Neurological manifestations	Aseptic meningitis, encephalitis, seizures	Moderate-high	High	Prompt immunosuppression and biologic therapy	(20, 55)
Pulmonary manifestations	Severe lung disease, ARDS, PAH	High	High	Aggressive immunosuppression and close monitoring	(7, 64, 65, 78)
Liver manifestations	Fulminant hepatitis, acute liver failure	High	High	Rapid escalation of therapy	(79, 80)
Haematologic manifestations	TMA, TTP, severe cytopenias	Very high	Very high	Urgent MAS work-up and intensive treatment	(6, 94, 97)
Ocular manifestations	Uveitis, Purtscher-like retinopathy	Low-moderate	Variable	Ophthalmologic assessment and systemic treatment	(104, 109)
ENT manifestations	Dacryoadenitis, trochleitis, septal perforation	Low	Moderate	Early anti-inflammatory treatment	(112, 113, 114)

downstream tissue-specific inflammatory responses (137). In this model, the nature, intensity, timing, and persistence of environmental triggers may influence which inflammatory pathways predominate in a given individual. Different infectious agents, microbial communities, environmental exposures, or inflammatory insults may preferentially promote activation of specific cytokine axes leading to distinct patterns of immune dysregulation (138, 139). When superimposed on a heterogeneous polygenic background, these differences may contribute not only to disease initiation but also to the selective involvement of specific organs and tissues in leading to different unusual manifestations. This framework may also explain why some patients develop predominantly systemic manifestations while others present with uncommon involvement of the cardiovascular, pulmonary, neurological, hepatic, renal, or haematological systems. Likewise, it may account for the marked geographical variability observed in the prevalence of certain rare manifestations, suggesting that environmental factors could act not merely as disease triggers but also as key modifiers of disease expression. Consequently, the clinical heterogeneity of AOSD likely reflects the existence of multiple gene-environment interaction patterns that converge on a shared inflammatory phenotype while generating distinct clinical trajectories, organ-specific complications, and degrees of disease severity. In this regard, AOSD shares several mechanistic features with monogenic autoinflammatory syndromes, although disease expression in AOSD appears to require the combined effect of multiple low-penetrance genetic variants and environmental co-factors (140-142). The convergence of these factors ultimately determines not only disease onset but also the severity and development of atypical manifestations, positioning AOSD within a continuum of cytokine-driven disorders characterised by variable penetrance, marked clinical heterogeneity, and a risk of life-threatening hyperinflammation (140-142).

From a clinical point of view, the recognition of these uncommon presentations is of particular importance (Table II), as several manifestations may be associated with substantial morbidity and mortality (Table III). Increased awareness among clinicians may facilitate earlier diagnosis, prompt therapeutic intervention, and improved patient outcomes. The available evidence remains largely based on case reports and small observational studies, reflecting the rarity of these manifestations and the challenges associated with studying uncommon disease phenotypes. Consequently, further multicentre studies and international collaborative registries are needed to better define their frequency, prognostic significance, and optimal management.

Conclusions

AOSD is increasingly recognised as a heterogeneous systemic inflammatory disorder characterised by a clinical spectrum that extends far beyond its classical triad of fever, rash, and inflammatory joint involvement. Although uncommon, rare and atypical manifestations may involve virtually any organ system and occasionally represent the initial or predominant presentation of the disease. Many of these infrequent manifestations may mimic infectious, neoplastic, or other autoimmune conditions, contributing to diagnostic uncertainty and delays in the initiation of appropriate treatment. Therefore, rare and atypical manifestations represent an important yet often underrecognized component of the AOSD disease spectrum. Greater awareness of these clinical entities may improve diagnostic accuracy, reduce delays in treatment, and ultimately contribute to a more comprehensive understanding of this complex autoinflammatory disorder.

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