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Review Article

Autoinflammatory syndromes: A review

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ABSTRACT

Autoinflammatory syndromes (AIS) are disorders of innate immunity which present with recurrent episodes of fever and skin lesions, such as urticaria, pustules, maculopapular rash, oral ulcers, generalized pustular psoriasis, or pyoderma gangrenosum-like lesions. The different entities that come under AIS are familial Mediterranean fever, tumor necrosis factor receptor-associated periodic syndrome, hyperimmunoglobulinemia D with periodic fever syndrome, and cryopyrin-associated periodic syndromes. Many new entities are also described. As many of them present with skin lesions, dermatologists should be aware of myriad of clinical features associated with these disorders. Childhood onset, positive family history, and elevated laboratory markers of systemic inflammation during acute episodes are the clues to diagnosis. Infections, connective tissue diseases, and malignancies should be excluded before diagnosing AIS.

Keywords: Autoinflammatory syndromes, Inflammasomes, Cryopyrinopathies, Familial Mediterranean fever, Tumor necrosis factor receptor-associated periodic syndrome

INTRODUCTION

Autoinflammatory syndromes (AIS) are enigmatic and diagnostic challenges for clinicians [Table 1]. These are rare disorders often having a striking-onset and manifest inflammatory features without an infectious or autoimmune cause. Genetically driven dysregulated innate immune response with the activation of inflammasome and excess of cytokines leads to the development of these disorders.[1-3] This differs from classical autoimmunity since, unlike autoimmune diseases, the primary pathogenesis of AIS does not involve antibodies or T-cell-mediated pathways or major histocompatibility complex-related processes.

Recurrent febrile episodes accompanied by cutaneous, mucosal, serosal, and osteoarticular manifestations, hepatosplenomegaly, lymphadenopathy, elevated acute-phase reactants, neutrophilia, and long-term risk of secondary amyloidosis characterize AIS. Cutaneous manifestations in AIS often warrant dermatology evaluation; hence, dermatologists should be aware of these syndromes and their varying presentations to diagnose and evaluate the patients.

Many may present with skin lesions (urticaria, pustules, maculopapular rash, oral ulcers, generalized pustular psoriasis, pyoderma gangrenosum, and Sweet's syndrome-like lesions). Infections, connective tissue diseases, and malignancies as the causes of recurrent fever need to be evaluated and ruled out before considering the possibility of AIS. Other clues to diagnosis are childhood onset, positive family history, and raised laboratory markers of systemic inflammation during the episodes.

Table 1: Autoinflammatory syndromes.

Disease	Inheritance pattern and most common age at presentation	Type of fever	Skin lesions	Systemic features	Others	Treatment
TRAPS	Autosomal dominant, TNF R 1 gene, infants adults	Usually 1–3 weeks	Erythematous rash or dermal plaques on extremities	Myalgia, arthralgia	Serositis, abdominal pain, conjunctivitis, periorbital edema	Etanercept Anakinra
FMF	Autosomal recessive, MEFV gene, <20 year in 80% of patients	≥39°C 1–3 days	Erysipelas-like	Recurrent monoarthritis, tenosynovitis, arthralgias, myalgia	Abdominal pain, serositis, scrotal swelling	Colchicine, Anakinra
HIDS	Autosomal recessive, MVK gene, <2 years	3–7 days	Maculopapular rash, aphthous ulcers	Arthralgia Arthritis	Cervical adenitis, abdominal pain	Anakinra
FCAS	Autosomal dominant, NLRP3, <1 year	<24 h	Urticaria	Arthralgias	Cold-induced conjunctivitis	Anakinra
MWS	Autosomal dominant, NLRP3 variable; infants, teens, young adults	Low-grade fever 1–3 day	Erythematous rash, urticaria (sometimes cold-induced)	Myalgias, arthralgias, arthritis	Conjunctivitis, uveitis, sensorineural hearing loss, fatigue	Anakinra
NOMID	Sporadic, NLRP3, <1 year	Mild fevers, constant	Chronic urticarial-like skin rash	Arthralgia, arthritis, bony overgrowth of epiphysis, bony hypertrophy/ deformity, frontal bossing	Chronic uveitis Conjunctivitis, chronic aseptic meningitis, sensorineural hearing loss, headaches, papilledema, optic atrophy, visual loss, mental retardation	Anakinra
AOSD/ SOJIA	Acquired; no known genetic link 3–35 years	≥39°C, daily quotidian fevers	Evanescent pink rash, 30–40% pruritic or urticarial	Polyarthritis Polyarthralgia Myalgia	Prodromal sore throat, serositis, lymphadenopathy, hepatosplenomegaly	Steroids Methotrexate Anakinra (IL-1 inhibitors)
PFAPA	Unknown 5–35 years	Lasting 4–5 days	Aphthous ulcerations	None	Pharyngitis cervical adenitis, abdominal pain	Tonsillectomy Single steroid dose Cimetidine Anakinra
PAPA	Autosomal dominant, PSTPIP1 gene, Children adolescents adults	None	Acne Pyoderma gangrenosum Pathergy	Inflammatory arthritis mostly large joints (some erosive or deforming)		TNF inhibitors IL-1 inhibitors
Cyclic neutropenia	Autosomal dominant, neutrophil elastase gene (ELA-2 or ELANE) Child to adult	10–14 day of low-grade fevers; recurs q 4–6 weeks	Oral ulcers gingivitis periodontitis recurrent cellulitis or furunculosis	None	Malaise, pharyngitis, lymphadenopathy	G-CSF, steroids
DIRA/ DITRA	AR, Loss of IL 1 receptor antagonist, Neonates		Generalized pustular psoriasis, aseptic pustular dermatitis		Multifocal osteomyelitis, and periostitis	Anakinra

(*Contd...*)

Table 1: (*Continued*).

Disease	Inheritance pattern and most common age at presentation	Type of fever	Skin lesions	Systemic features	Others	Treatment
Schnitzler syndrome	50 years or older	Recurrent fever	Nonpruritic urticated macules, papules or plaques	Bone or joint pain especially over the ilium or tibia, lymphadenopathy, hepatosplenomegaly	B-cell lymphoproliferative disorder	Colchicine, NSAIDs, HCQs, and anakinra

TRAPS: TNF receptor-associated periodic syndrome, FMF: Familial Mediterranean fever, HIDS: Hyperimmunoglobulinemia D with periodic fever syndrome, FCAS: Familial cold autoinflammatory syndrome, MWS: Muckle–Wells syndrome, NOMID: Neonatal-onset multisystem inflammatory disease, AOSD/SOJIA: Adult-onset still disease, PFAPA: Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy, PAPA: Pyogenic arthritis, pyoderma gangrenosum, acne. DIRA/DITRA: Deficiency of the IL-1 receptor antagonist (IL-1Ra)/Deficiency of the IL-36R antagonist

Monogenic autoinflammatory diseases

These groups of illnesses typically manifest in childhood. They are caused by single-gene defects in innate immune regulatory pathways. They can mimic infections clinically; the aseptic nature of inflammatory lesions favors AIS over infections. Affected individuals often have first- or second-degree relatives with similar features. A monogenic defect has been identified for familial Mediterranean fever (FMF), tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), and cryopyrin-associated periodic syndromes (CAPS).

CAPS include a spectrum of disorders – familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID).

Additional disorders manifesting similar inflammatory features without an identifiable genetic cause are also grouped under AIS. Etiologic defects have been discovered for cyclic neutropenia, pyogenic arthritis-pyoderma gangrenosum-acne (PAPA) syndrome, pyoderma gangrenosum-acne-suppurative hidradenitis (PASH) syndrome, deficiency of the IL-1 receptor antagonist (IL-1Ra) (DIRA), and deficiency of the IL-36R antagonist (DITRA). Those without a known cause include systemic-onset juvenile idiopathic arthritis (SOJIA), adult-onset Still's disease (AOSD), periodic fever-aphthous stomatitis-pharyngitis-and-adenopathy (PFAPA) syndrome (or Marshall syndrome), and Schnitzler syndrome.[1-5]

Pathogenesis

A disrupted and dysregulated innate immunity leads to the development of AIS. AIS are also known as inflammasomopathies owing to the involvement of inflammasomes in this disorder.[6]

The inflammasome, like the Toll-like receptor, is a critical part of the normal innate immune response to infection and tissue injury. These are cytoplasmic protein complexes involved in the regulation of processing of IL-1β and the progression of the inflammatory cascade. They have been described in myeloid cells as well as in epithelial cells, including keratinocytes. A number of these cytosolic receptors have been identified, such as the NOD-like receptor (NLR) family of receptors NOD-like receptor pyrin domain-containing (NLRP)-3, NLRP1, AIM2, and MEFV. The expression of NLRP3, NLRP1, and AIM2 has been identified in keratinocytes.[7,8] When activated, these cytosolic receptors oligomerize with an adaptor protein called Apoptosis-associated speck-like protein containing CARD (APC) and caspase-1 to form the inflammasome complex. Assembly of the inflammasome complex leads to the activation of caspase-1, which activates multiple substrates but most importantly the precursor to

IL-1β, leading to production of active IL-1β. Mutations in the genes encoding components of inflammasomes lead to dysregulation of the IL-1 inflammatory cascade and result in monogenic autoinflammatory diseases.[9,10]

Activation of inflammasome also yields increased production of other pro-inflammatory cytokines, such as IL18, TNF alpha, IL6, IL17, IFN alpha and beta, and the complement system.

TRAPS

TRAPS is also called familial Hibernian fever due to high frequency of incidence in people of Irish, Scottish, Austrian, or Northern European descent. It is characterized by febrile attacks that last for 1–3 weeks and occasionally up to 6 weeks. The clinical features include fever, arthralgia, myalgia, migratory rash, abdominal pain, pleuritis, conjunctivitis, periorbital edema, oral ulcers, and scrotal swelling. Skin manifestations include migratory macular erythematous rash or patches, ecchymoses, edematous dermal plaques, serpiginous or annular lesions, and periorbital edema.

The genetics underlying this was studied in large multiplex Irish families who had an AD syndrome characterized by recurrent fever, rash, and abdominal pain. Vast majority had childhood onset at around 3 years, but adult onset may occur. The disease develops due to mutation of the gene encoding P55 TNF receptor type 1. There are 46 missense mutations involving TNF receptor type 1 which are localized to distal chromosome 12 p. Etanercept is an effective treatment which reduces the frequency and severity of flares in TRAPS.[11,12]

FMF

It is the most common autoinflammatory disease. It preferentially affects the Sephardic Jews, Armenians, Turks, Arabs, and Moroccans whose familial origin can be traced to the Mediterranean basin. However, it has been diagnosed in non-Mediterranean as well. It begins in childhood or adolescence, and up to 20% may have their first attack after the age of 20 years. Febrile episodes are accompanied by cutaneous, serosal, synovial, or tenosynovial inflammation. Fever is high grade and lasts for 1–3 days. Bouts are unpredictable in frequency and may be provoked by infection, stress, exercise, or surgery. Cutaneous features are rather unilateral than bilateral. Erysipelas-like erythema located on the extensor surface of arms and legs or dorsum of feet which is often painful is a characteristic feature. Recurrent inflammatory, sterile monoarticular inflammation, joint effusion, or tenosynovial swelling may also occur. Serositis manifests as peritonitis, pleuritis, pericarditis, or scrotal swelling. Aseptic meningitis is a rare manifestation. Leukocytosis and elevated ESR and CRP are the laboratory abnormalities noted. Amyloidosis may complicate FMF as serum amyloid A gets deposited in kidneys or other organs. It results from a recessive mutation of the MEFV (Mediterranean fever gene 16p13) located on short arm of chromosome 16. There are more than 80 missense mutations. MEFV is found in neutrophils and myeloid cells and encodes 86 KDa protein called pyrin. Defective pyrin function leads to uncontrolled inflammation with elevated levels of IFN gamma and pro-inflammatory cytokines like TNF alpha, and interleukins (IL) 1, 6, and 8. Colchicine controls the attacks and prevents amyloidosis. Refractory cases respond to IL-1 inhibitor anakinra. Combination of recurrent bouts of fever with synovial, serosal, or cutaneous inflammation and elevated acute-phase proteins should raise the suspicion of FMF.[13]

HIDS

HIDS and mevalonic aciduria (MA) represent the two ends of a clinical spectrum caused by deficiency of mevalonate kinase (MVK), an enzyme involved in the cholesterol and isoprenoid biosynthetic pathway.[14] Complete deficiency induces MA while partial deficiency manifests with recurrent fever and usually but not always with overproduction of immunoglobulin D (HIDS).[15] The median age of onset of disease ranges from 1st week of life to 10 years. Inheritance pattern is AR. In HIDS, the clinical picture is dominated by recurrent febrile attacks lasting for 3–7 days with headache, polyarthralgia, abdominal pain, diarrhea, and bilateral tender cervical adenopathy.[16] Two-third of the patients with HIDS manifest an eruption with fever. Erythematous macules, maculopapular rashes, urticaria, purpura, erythema nodosum, and oral and genital aphthae are the observed features in the affected. Immunization, surgery, trauma, and stress are the classical triggering factors. Similar to HIDS, patients with MA present with febrile episodes and systemic inflammation, but other features include severe failure to thrive, developmental delay, hepatosplenomegaly, anemia, dysmorphic facies, and cerebellar ataxia. The diagnosis of HIDS is usually suspected clinically, but definitive diagnosis is made by genetic testing, while MVK gene analysis is the gold standard testing. IgD levels are more than 100 IU/dl. Fever and arthralgia may respond to NSAIDS, but colchicine is usually ineffective. Anakinra, an IL-1 receptor antagonist, has been effective in reducing the clinical and biochemical inflammation in MA. Canakinumab, a long-acting monoclonal antibody against IL-1β, anti-TNF agents, and HMG-CoA reductase inhibitors are found useful in some cases.[17]

CAPS

Cryopyrinopathies are rare autoinflammatory diseases that present with recurrent bouts of systemic inflammation involving chiefly skin and joint.[18] It comprises a spectrum of diseases caused by a defect of NLRP3 (NOD-like receptor family, protein pyrin domain containing protein 3; or cryopyrin) functions and is inherited in an autosomal dominant fashion.[19] Three closely related phenotypes that

are included under cryopyrinopathies are FCAS, MWS, and chronic infantile neurological cutaneous articular syndrome (CINCA)/NOMID. Among these, FCAS is the mildest form and CINCA is the most severe. CAPS mainly occurs in pediatric age group.[20]

Skin involvement is found in all three diseases, and most cases usually present with skin rash. Nonpruritic urticarial lesions appear on the trunk and limbs, but a few may report a burning sensation.[21] Lesions are usually migratory in nature and last for <24 h.[22] This urticarial rash differs from classical urticaria and shows dermal perivascular infiltrate composed of neutrophils instead of the typical lymphocytic and eosinophilic infiltrate observed in urticaria. Therefore, the term neutrophilic urticarial dermatosis is used for this manifestation.[23]

FCAS

This entity is characterized by recurrent self-limiting episodes of low-grade fever, urticarial rash, arthralgia, and conjunctivitis which are precipitated by cold exposure. Patients may also present with nausea, drowsiness, extreme thirst, sweating, and headaches.[24] Symptoms usually begin within 1–2 h of cold exposure and attacks lasts for <24 h.[1] Most of the patients present before 6 months of age.[25]

MWS

This syndrome is characterized by recurrent episodes of fever, rash, arthralgia, headache, and conjunctivitis. Sensorineural deafness occurs in about 70% and may appear in childhood or early adulthood.[26] Secondary amyloidosis due to chronic inflammation is the most serious complication that may develop in about 25% of the affected.[27]

CINCA/NOMID

A triad of arthropathy, urticaria, and CNS involvement is the hallmark of CINCA. CNS manifestations can occur in almost all patients and range from aseptic meningitis to increased intracranial pressure and cognitive impairment. Sensorineural deafness is found in 75% of patients and is detectable in the first decade of life.[28] Bone and joint inflammation lead to severe and disabling arthropathy in one-third cases. Renal amyloidosis is rare in these patients. Compared to other cryopyrinopathies, CINCA is associated with an increased mortality rate when compared to other AIS.

Still's disease

It affects children below 16 years or adults aged 18–35 years.

AOSD or Wissler–Fanconi syndrome is a systemic inflammatory disorder of unknown etiology characterized by spiking fever, evanescent skin rash, arthralgia or arthritis, involvement of various organs, and predominantly neutrophilic leukocytosis.[29,30]

Diagnosis of adult-onset Still's disease is based on Yamaguchi's criteria.[31]

Major criteria

- Fever of ≥39°C, lasting ≥1 week.
- Arthralgia lasting ≥2 weeks.
- Typical rash (macular or maculopapular nonpruritic salmon-pink eruption usually appearing during fever).
- Leukocytosis (≥10,000/mm^3) including 80% or more of granulocytes.

Minor criteria

- Sore throat.
- Lymphadenopathy and/or splenomegaly.
- Liver dysfunction.
- Negative rheumatoid factor and negative ANA.

Exclusions

- Infections (especially sepsis and infectious mononucleosis).
- Malignancies (especially malignant lymphoma).
- Rheumatic diseases (especially polyarteritis nodosa and rheumatoid vasculitis with extraarticular features).

Diagnosis of AOSD requires ≥5 criteria including ≥2 major criteria. Patients who have AOSD commonly present with fever which is classically described as quotidian, with temperature spiking once a day to 39°C or higher, usually in the evening or at night. The typical Still's rash is asymptomatic macular or maculopapular and has a characteristic salmon-pink color.

SOJIA occurs in children and the presentation is similar to AOSD with spiking fever and maculopapular rash. Arthritis is considered essential to diagnose SOJIA. In a subset of patients, in addition to evanescent salmon-pink rash on the trunk and lower legs, more persistent pruritic papules, and plaques develop on the trunk, neck, face, or extensor aspect of the limbs. Methotrexate is used in the management, but anakinra is preferred in the systemic variant. Macrophage activation syndrome is a fatal complication that warrants specific cytokine inhibitor therapy with TNF blocker adalimumab.[29]

Schnitzler syndrome

Schnitzler syndrome usually manifests in adults aged 50 years or older. It is characterized by chronic urticarial eruption and persistently raised monoclonal IgM with at least two of the following features: recurrent fever above 40°C, bone or joint pain, especially over the ilium or tibia, lymphadenopathy, hepatosplenomegaly, neutrophilia, increased acute phase

reactants, and abnormal bone imaging. Skin lesions include nonpruritic urticated macules, papules, or plaques, especially on the trunk which resolve with brownish pigmentation. 15–20% of the affected develop B-cell lymphoproliferative disorder. Strasbourg diagnostic criteria are used to diagnose the condition. The treatment options include colchicine, NSAIDs, HCQs, and anakinra in severe cases.[29]

PAPA

Mutation in PST P1P1 gene is recognized as the cause for this autosomal dominant disease. Hyperphosphorylated PSTP1P1 protein causes prolonged binding to pyrin, and this prevents inhibitory action of pyrin on NLRP 3 inflammasome. This, in turn, leads to the elevation of IL-1b and inflammation ensues. Manifestation begins in early childhood with recurrent painful sterile, pauciarticular, and nonaxial arthritis precipitated by trauma. It may occasionally lead to significant joint destruction. By puberty, joint symptoms subside and skin lesions appear. Severe nodular acne, hidradenitis suppurativa, pyoderma gangrenosum and positive pathergy are the other features. PAPASH is characterized by pyogenic arthritis, pyoderma gangrenosum, acne and suppurative hidradenitis. PASH include pyoderma gangrenosum, acne and suppurative hidradenitis. Anakinra and anti-TNF alpha agents are used in treatment.[29]

Blau syndrome

Blau syndrome is also called autoinflammatory granulomatosis of childhood. It follows an AD pattern of inheritance. The syndrome is due to mutation in CARD 15 gene. NOD 2 is a member of a family of pattern recognition receptors involved in innate immune defense against invading pathogens. The usual manifestation of disease (chronic granulomatous polyarthritis and rash) is seen before the age of 4. The affected joints are peripheral. Uveitis is seen in 80% of cases. Widespread skin-colored or yellowish-brown papular eruption that fades to leave pitted scars is the typical rash. Noncaseating granulomatous inflammatory infiltrate in the dermis is the histopathology feature of rash.

DIRA and DITRA

DIRA and DITRA are rare autoinflammatory disorders due to deficiency of IL-1 receptor antagonist and IL-36 receptor antagonist, respectively. Loss of the IL-1R antagonist leads to unopposed pro-inflammatory signaling by IL-1α and IL-1β in patients with DIRA. In DITRA, loss of the IL-36R antagonist results in similar unchecked signaling by IL-36α, IL-36β, and IL-36γ at the IL-36R.

The cutaneous and systemic features of DIRA bear similarity to features seen in pustular psoriasis and synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome.[32,33]

The disease manifests in neonates with fever, aseptic pustular dermatitis, multifocal osteomyelitis, and periostitis. Grouped pustules that subsequently develop yellow crusts appear on an erythematous base in the newborn or within the first 3 weeks of life.

DITRA is a recently described autoinflammatory disease characterized by repeated flares of generalized pustular psoriasis, high fever, asthenia, and systemic inflammation. Inheritance is autosomal recessive. There are reports of successful treatment of DITRA with anakinra.[34]

Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE)

CANDLE was first reported from Japan as Nakajo–Nishimura syndrome due to abnormal signaling in IFN pathway. This is due to mutation in PMSB8 gene. Children present with recurrent fever, rash, arthralgia, and arthritis. Starting within 2–3 weeks of birth, the disease shows an episodic course during the 1st year of life with violaceous or erythematous, often annular and edematous plaques on the face, trunk, and interphalangeal joints. Lesions resolve with purpura or pigmentation. Other features include persistent, violaceous, periorbital edema, swelling of fingers and toes, and recurrent episodes of panniculitis, which manifest as lipoatrophy. CANDLE is a serious disorder with no known therapy, and up to 50% die before adulthood.

Majeed syndrome

Majeed syndrome is characterized by recurrent episodes of fever and inflammation in the bones and skin. Dr. Majeed recognized this as a distinct autosomal recessive disorder in 1989.[35]

There are two main features of Majeed syndrome: Chronic recurrent multifocal osteomyelitis (CRMO) is an inflammatory bone condition, which manifests with recurrent episodes of pain and joint swelling. The symptoms begin in infancy or early childhood and typically persist into adulthood. Short periods of improvement may be there. CRMO may lead to complications such as slow growth and joint deformities (contractures), which restrict the movement of certain joints.

Congenital dyserythropoietic anemia is a blood disorder that presents as shortage of red blood cells. The resulting symptoms include tiredness (fatigue), weakness, pale skin, and shortness of breath.

The original report described three members of a consanguineous Arab family, who had CRMO, congenital dyserythropoietic anemia, and neutrophilic dermatosis. Majeed syndrome is a pyogenic autoinflammatory disease caused by autosomal recessive loss-of-function mutations in the LPIN2 gene encoding the protein lipin-2. It is unresponsive

to treatment with antibiotics and may respond to NSAIDs, corticosteroids, IFN-γ, bisphosphonates, and anti-TNF drugs. Recently, the efficacy of IL-1 inhibition with either anakinra or canakinumab was demonstrated in two brothers with Majeed syndrome who showed no response to anti-TNF therapy.

Most people with Majeed syndrome also develop Sweets syndrome like lesions.

OTHER AUTOINFLAMMATORY DISORDERS

PFAPA - Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy. It is the most common periodic fever syndrome during childhood. Marshall syndrome or PFAPA syndrome was first described by Marshall *et al*. in 1987.[36] Characteristically, it begins during childhood, commonly between 2 and 5 years of age, and resolves before the end of first decade. There is a slight male predominance.[37,38] Patients present with abrupt episodes of fever that last for 3–6 days and recur every 3–4 weeks and may associate with one or more of the following symptoms: aphthous stomatitis, exudative or nonexudative pharyngitis, tender cervical lymphadenopathy, and mild abdominal pain. Other less specific symptoms are fatigue, myalgias, and headache.

In children with PFAPA, periodic fever rather than stomatitis is the primary complaint.[39]

An important differential diagnosis of PFAPA syndrome is cyclic neutropenia, also characterized by recurrent fever, oral aphthae, pharyngitis, and lymphadenopathy. In addition, cyclic neutropenia patients also manifest intermittent neutropenia (<500/mm^3) during febrile episodes which put them at risk of infection. The gene neutrophil elastase is mutated in cyclic neutropenia.[40]

CONCLUSION

AIS are a group of rare disorders of innate immunity characterized by repeated episodes of inflammation without an obvious cause. Many of these disorders have a childhood onset and present with recurrent fevers, skin lesions, joint pains, and other systemic features. Several of these have distinctive cutaneous manifestations, and dermatologists have an important role in diagnosing these conditions. Recently, molecular basis for many of these diseases has been identified, thus paving the way for novel targeted therapies. IL-1 blockers have been found to be more effective than the conventional immunosuppressants in their treatment.

There is not one clinical symptom, but rather a set of symptoms occurring repeatedly which suggests the diagnosis of AIS. Urticaria is a common presenting feature of AIS and has to be differentiated from ordinary urticaria. GPP, erysipelas-like lesion, and maculopapular rash may also be the presenting features.

Declaration of patient consent

Not required as there are no patients in this article.

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Conflicts of interest

There are no conflicts of interest.

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