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Distal lower extremity swelling as a prominent phenotype of NOD2-associated autoinflammatory disease

Sir, We previously reported an autoinflammatory disease associated with nucleotide-binding oligomerization domain containing protein 2 (NOD2) gene mutations, designated as NOD2-associated autoinflammatory disease (NAID) [1, 2]. Herein we report the presence of distal lower extremity (ankle and foot) swelling as a prominent phenotype of this disease.

Five patients were recruited as they met diagnostic criteria for NAID [2] and had a clinical commonality: distal lower extremity swelling/pain. The consent of the patients was obtained and the study was approved by the Institutional Review Board of the Cleveland Clinic.

Patient 1, a 64-year-old white woman, presented with intermittent fever with maximum temperature of 39.4°C and each episode typically lasted 2 days followed by abdominal erythematous patches. These symptoms had recurred every 4 weeks during the previous 5 years, with each episode lasting for several days. A skin biopsy showed dermatitis. There was also intermittent polyarthralgia, with notable left ankle and foot swelling; US examination excluded deep vein thrombosis (Fig. 1A); radiographic examination was unremarkable. Oesophagogastroduodenoscopy (EGD) and colonoscopy with biopsy were performed for heartburn, but the results were unremarkable.

Patient 2, a 47-year-old white woman, had intermittent erythematous patches and plaques on the face and neck. They had recurrent every 6 weeks for the past 3 years, and each episode lasted for 5–7 days. A skin biopsy showed spongiotic dermatitis. She also had intermittent polyarthralgia, particularly unilateral ankle and foot swelling, on both physical and radiographic examination. A workup for mild diarrhoea, including EGD, colonoscopy and CT enterography, was unremarkable.

Patient 3, a 49-year-old white woman, presented with intermittent erythematous rash on her extremities over the past 6 years. She also had intermittent polyarthralgia, with notable ankle and foot swelling with unremarkable radiograph, and each episode of the articular presentation lasted for a few hours to 3 days. Besides low-grade fever, she also had intermittent moderate left upper quadrant pain, which prompted a workup including chest radiograph, EGD and CT scan of the abdomen and pelvis. The results were normal as were her serum lipase and amylase levels.

Patient 4, a 29-year-old white man, presented with multiple episodes of bloody stools and abdominal pain of 1 month duration. His father had been diagnosed with colitis but did not have any known NOD2 mutations. A colonoscopic examination with biopsy showed non-specific pancolitis with normal terminal ileum and the absence of granulomas. The patient reported left lower chest pain, and a chest radiograph and CT revealed left lower lobe infiltrate with a small pleural effusion, which resolved with several days of high-dose prednisone. He also had right foot/ankle redness and swelling (Fig. 1B) and transient freckle-like rash on the extremity. A skin biopsy showed leucocytoclastic vasculitis (LCV).

Patient 5, a 52-year-old white woman, reported high fever of 3 years’ duration; it recurred every 10 days, and each episode lasted for several hours. She also had intermittent polyarthralgia with notable ankle swelling and pain

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bilateral. A MRI of the ankle demonstrated moderate s.c. oedema, particularly within the pre-Achilles fat (Fig. 1C and D). She also had itchy red spots on her thigh and arm. There were no gastrointestinal symptoms other than constipation, and a colonoscopic examination was normal.

Of the five patients, four had constitutional symptoms and three had sicca-like symptoms, but the results of serological testing and minor salivary gland tissue biopsy were normal. There was no evidence of uveitis, respiratory symptoms or hilar adenopathy on chest radiographs in any of these five patients. None of the patients had a family history of periodic fever syndrome, and all carried the NOD2 variants, with four having concurrent IVS8+158 and R702W and one with a rare NOD2 variant, heterozygous T189M.

Among the NOD2-associated diseases [3], NAID is a newly recognized disease characterized by recurrent fever, dermatitis, inflammatory arthritis, gastrointestinal and sicca-like symptoms, and it is presently associated with the NOD2 variants IVS8+158, R702W [1, 2] and R703C [4]. Our case series suggests that distal lower extremity swelling is a prominent clinical phenotype of NAID although this type of swelling may also occur in several other rheumatic disorders. Sarcoidosis can cause ankle and foot swelling which is often associated with Lofgren syndrome [5].

Only a single case of Crohn’s disease was reported to develop ankle swelling with the presence of LCV of both lower extremities [6], yet the NOD2 status was unmentioned.

Of note, patient 5 carried the variant T189M, which in one study was found in 0% (0/906) of patients with Crohn’s disease vs 0.97% (2/206) of healthy controls [7]. It has never been reported in association with Blau’s syndrome. Given the similar phenotype, we believe that this patient had NAID. The skin disease of our patients is mostly compatible with dermatitis as previously reported [2]. Altogether, distal lower extremity swelling is one of the characteristic phenotypes of NAID.

Rheumatology key message

- Lower extremity swelling/pain is one of the phenotypic features of NOD2-associated autoinflammatory disease.
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Pure ocular mucous membrane pemphigoid in a patient with axial spondyloarthritis (HLA-B27 positive)

Sin, Here we describe to the best of our knowledge the first case of pure ocular mucous membrane pemphigoid (POMMP) as an ocular manifestation of axial spondyloarthritis (SpA). A 58-year-old male veteran was seen in the ophthalmology clinic for progressive vision loss and possible bilateral symblephara. His medical history was significant for hypertension, diabetes mellitus type 2 and dyslipidemia. At the initial visit, the patient’s corrected distant visual acuity was 20/25 —1 in the right eye and 20/40 +1 in the left eye. Slit lamp examination was significant for conjunctival injection and bilateral temporal symblephara was noted on the initial visit. Differential diagnosis included POMMP, Stevens–Johnson syndrome and sequela of adenoviral conjunctivitis. For the first 3 months the patient was treated with various topical agents, including fluorometholone drops, prednisolone suspension, tacrolimus ointment as well as high-dose oral prednisone, without relief. His ocular condition had deteriorated significantly, with the formation of marked symblepharon OU with inferior fornical shortening and a small pannus of conjunctival tissue extending into the inferior aspect of the cornea on the right (Fig. 1A–D).

Pathological examination of a biopsy from the conjunctiva was remarkable for subepithelial bullae on haematoxylin and eosin staining (H&E; Fig. 1E). Direct immunofluorescence revealed faint linear IgA basement membrane deposits. The patient was diagnosed with POMMP and sent to the rheumatology clinic for further diagnostic and therapeutic evaluation.

On deeper interrogation in the rheumatology clinic, a history of non-steroidal anti-inflammatory responsive lumbar spinal pain and unilateral right buttock pain that worsened with rest and improved with activity since his teenage years was elicited. The patient also reported a history compatible with bilateral Achilles tendon enthesisitis, plantar fasciitis and bilateral swelling of his fingers and toes in the past (possible dactylitis). There was no history of a diagnosis of psoriasis or IBD nor did the peripheral joints demonstrate active synovitis on physical examination. Investigations demonstrated a positive HLA-B27 allele and autoantibody assessment was negative for RF, anti-CCP, ANA, anti-ENA panel, anti-dsDNA and perinuclear/cytoplasmic ANCA. Bilateral grade II sacroiliitis (Fig.1F) was noted on radiographic examination. A diagnosis of undifferentiated axial SpA (HLA-B27 positive) was rendered based on the Assessment of SpondyloArthritis international Society (ASAS) criteria [1].

The patient was started on MTX, and the dose was titrated up to 25 mg s.c. injections once a week over 3 months, under close clinical and laboratory surveillance. Both the POMMP and the peripheral musculoskeletal symptoms of SpA have responded well to this therapy.

SpA is a group of chronic systemic inflammatory rheumatic diseases including AS, PsA, enteropathic arthritis, reactive arthritis, undifferentiated SpA and juvenile SpA. Although characterized by inflammation and new bone formation in the axial skeleton, SpA can also involve peripheral joints, entheses and other organs such as the eyes, skin, heart and gut [1, 2]. Although ocular involvement in SpA typically takes the form of acute anterior uveitis (AAU), occurring in 25–40% of patients at some point in the disease course [3, 4], rarer manifestations may include anterior scleritis, posterior scleritis and hypotony maculopathy [5].