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Early onset sarcoidosis (Blau syndrome): erosive and often misdiagnosed

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- **Key message:** Although uncommon, early severe radiological joint erosions do not preclude a diagnosis of EOS/Blau syndrome.

Dear Editor, early-onset sarcoidosis (EOS) is an uncommon paediatric onset arthritis caused by denovo mutation of *NOD2*; its rarity lends itself to misdiagnosis with Systemic Juvenile Idiopathic Arthritis (SJIA). EOS when inherited via an autosomal dominant pathway is termed Blau syndrome, the two conditions are clinically identical. Deforming arthritis in the absence of significant radiographic erosions has been cited as a distinguishing feature of EOS. We report a case of proven EOS demonstrating clear evidence of progressive radiographic erosions.

A 31 year old caucasian female diagnosed with SJIA in 1989 at 18 months, has been managed by our adult Rheumatology service since 2007. Our patients disease phenotype was composed of extensive deforming polyarthritis associated with bilateral panuveitis. Clinical examination revealed small joint synovitis as well as flexion contractures at the elbows. There has never been any cutaneous or nail changes. Eye examination showed the legacy of uncontrolled inflammatory activity with reduced visual acuity, bilateral vitritis and chorioretinal scarring. She had no significant family history.

Investigations reveal a negative rheumatoid factor, antinuclear antibody and anti-neutrophil cytoplasmic antibody alongside normal complement and elevated inflammatory markers. Hand radiographs 18 years after diagnosis showed widespread symmetrical erosive damage (Fig.1). Pelvic and spinal radiographs have never demonstrated features of axial spondyloarthropathy.

Disease activity remained high despite conventional disease modifying anti-rheumatic drugs (DMARDs) and biologic DMARDs, including: anti-TNF (infliximab, adalimumab, etanercept, certolizumab, golimumab); anti CD-20 (rituximab); anti IL-6 (tocilizumab) and anti IL-1 (anakinra) agents. Consequently, she has required continuous daily oral corticosteroids to limit progression.

Her son, aged 4 years old, developed a symmetrical polyarthritis with uveitis and fever and following this, was diagnosed with EOS/Blau syndrome. At this point our patient's diagnosis was reviewed. Genetic testing in our patient confirmed the c.1000C>T mutation in the *NOD2* gene (16q12.1) leading to the pathological p.R334W protein change. Subsequently, her diagnosis was changed to that of EOS and her son's confirmed as Blau syndrome.

EOS is a sporadic auto-inflammatory condition, clinically and pathophysiologically distinct from other forms of sarcoidosis (1), characterised by the clinical triad of arthritis, recurrent uveitis and granulomatous skin dermatitis. Blau syndrome describes the inherited form, phenotypically indistinct

from EOS; an initial genetic locus was located in 1996, with later localisation of this to the *CARD15/NOD2* region (2). Over 22 mutations of this gene have been identified, with p.R334Q and p.R334W found to account for a significant majority of EOS (3). It is thought that these mutations lead to *NOD2* protein activation following antigen exposure may initiate an activation cascade terminating in the activation of end proteins, such as NF-kappa B, implicated in the inflammatory pathway (4).

The largest observational study to date reported findings from 24 patients (13 children and 11 adults, equating to radiographs of 45 hands and wrists in total) with Blau (5). Significant abnormalities, for example carpal dysplasia and crowding, were seen, but were notable for the total absence of radiographic erosions. Not all patients recruited to the study had radiological findings discussed, nor have they recorded the characteristics of the patients used (i.e. specific *NOD2* genetic mutation), limiting interpretation of these findings to the whole EOS/Blau cohort; nonetheless this large study was unable to demonstrate erosive disease in these patients. Smaller reports again make no reports of patients with erosive disease (3, 6). Interestingly Blank et al (7) report one individual with radiographic erosions; alongside our case this suggests that EOS may be under recognised in the context of erosive disease.

EOS is a rare sporadic cause of paediatric onset arthritis that is heritable through an autosomal dominant pattern. Its correct identification has importance for prognostication, prediction of response to therapy and need for genetic counselling. We highlight the existence of severe erosive arthritis in EOS and the need to consider genetic testing in patients presenting with features of EOS.

Legend: Figure 1 The patients bilateral hands radiograph

Hands radiograph demonstrating various features of erosive inflammatory arthritis. Peri-articular osteopenia (white oval) is evident around all MCP, PIP and DIP joints. Erosive changes of the metacarpal heads (whit circles) with secondary degeneration and subluxation of the joints. Secondary osteoarthritis of multiple PIP, DIP and carpal joints is evident with resultant collapse of the carpal rows. Bilateral Madelung deformity where there is notching of the distal radius by the ulnar heads (white rectangle) secondary to growth plate arrest & shortening of ulna from episodes of juvenile inflammatory arthropathy.

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