problem area before and during the procedure (Fig. 1C). Ninety-two per cent of patients (24/26) felt that observing the US images in real-time helped with the process of having an injection. Of these 24 patients, 67% felt that observing the US images gave them additional information that helped to improve their understanding of the procedure, 54% of patients felt that the precise area that was causing the pain had been identified and 75% of patients felt that the injection would be aimed at the area causing the pain. If recommended, 95% of patients were very likely or somewhat likely to undergo a further US-guided procedure on the same joint or another inflamed joint (Fig. 1D). Among those who had had a non-guided injection previously (n = 19), 66% of patients felt that US-guided injections were much more effective or somewhat more effective compared with traditional injections (Fig. 1E). Overall, 58% of patients felt that their US-guided injections were much more effective or more effective compared with their expectations (Fig. 1B).

This pilot study has some limitations. No validated psychometric questionnaire was available for this specialized purpose, therefore we used a non-validated questionnaire to obtain retrospective views of patients. Furthermore, such a retrospective survey is vulnerable to response bias, potentially enhancing the number of overtly positive or negative responses.

Observing US images during the procedure improved the overall experience of this intervention. Observing the US images in real-time improved patients' understanding and tolerability of the procedure and reduced patients' anxiety. This is consistent with a randomised controlled study that suggested US guidance improved pain scores ($p < 0.001$) and overall response rate ($p < 0.01$) compared with traditional palpation-guided injection [7]. Anxiety level has been shown to be the strongest negative predictor of poor outcome following facet joint injections [8], indicating that the patient's level of anxiety affects treatment response.

A larger study is required to confirm our preliminary findings that US-guided injection improves the tolerability of the procedure and reduces patients' anxiety during the procedure. Further issues that require investigation include whether visualising real-time images during US scanning improves patients' understanding of disease pathology, which could lead to indirect benefits such as improving therapy adherence and improved pain management strategy.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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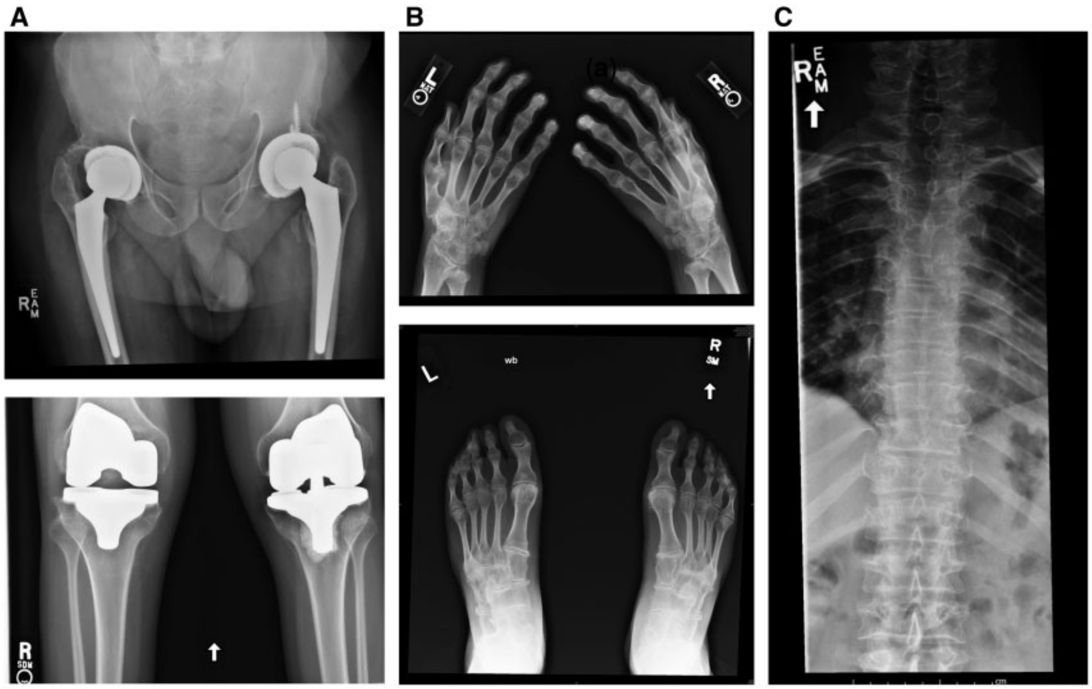
An argument for early genomic sequencing in atypical cases: a *WISP3* variant leads to diagnosis of progressive pseudorheumatoid arthropathy of childhood

Rheumatology key message

- Genomic sequencing increased phenotypic precision in a difficult-to-solve case of precocious osteoarthritis.

Fig. 1 Radiographic imaging studies



(**A**) Bilateral total hip (upper panel) and knee (lower panel) replacement. (**B**) Hands (upper panel) show diffusely demineralized bony structures with diffuse, advanced joint space narrowing of the proximal and distal IP and MCP joints bilaterally. Images of the feet (lower panel) are also notable for bilateral diffuse osteopenia and cartilage space narrowing in nearly all of the proximal and distal IP, MTP and tarsometatarsal joints. There is mild diffuse decreased mineralization with moderate tibiotalar and intertarsal joint space narrowing and osteophytes. No erosions were noted. (**C**) Images of the spine reveal diffuse platyspondyly with associated degenerative disc disease.

Sir, A 34-year-old Pathan male from Pakistan presented for evaluation of widespread musculoskeletal pain and multiple associated functional limitations. Musculoskeletal symptoms began at age 5 years and widespread polyarthritis ensued. Between the ages of 23 and 29 years, the patient underwent bilateral total hip replacements, bilateral knee replacements and two lumbar spine surgeries.

The patient's adult height was 58 inches, notable for a relatively short torso. His head was normocephalic with non-dysmorphic facies. His examination was notable for bony swelling and restricted motion of the proximal and distal IP joints of the fingers and toes, limited range of motion in the wrists, flexion contractures of the elbows, markedly limited range of motion in both shoulders and ankles and restricted range of motion in his cervical spine.

Serologic tests for RA were negative. X-rays demonstrated joint space narrowing and osteophytes without erosions at the proximal and distal IP and MCP joints of the hands, the intercarpal joints, the glenohumeral joints, the tibiotalar joints and the intertarsal joints (Fig. 1). Spinal imaging revealed platyspondyly and disk space narrowing.

The patient had been formerly incorrectly diagnosed with JRA, which was subsequently updated to a phenotype of precocious, degenerative polyarticular non-inflammatory osteoarthritis. Over 25 years, a more specific diagnosis had not been reached.

The family is consanguineous; the parents of the proband are half first cousins, so the parents share a common grandfather but have different grandmothers (Supplementary Fig. S1, available at *Rheumatology* Online). His family history was notable for one similarly affected sister (30 years old) and two affected cousins (not shown), five unaffected sisters and one unaffected brother. Inheritance is likely due to identity by descent, given the inheritance of two copies of an ancestral allele from the common great-grandfather, leading to autozygous regions.

Details about sequencing, alignment, variant calls and annotation are provided in the supplementary data section on genomic sequencing and alignment, available at *Rheumatology* Online. After reviewing nine recessive candidate variants, we found that the most likely causal variant is a homozygous frameshift variant in the *WISP3* gene at chr6:112389558_112389559 (GRCh38), where a CTG is expected, but a C is observed (NM_198239.1: c.794_795delGT (p.Cys265LeufsX31); see Supplementary Fig. S2, available at *Rheumatology* Online). This variant was selected as the most likely candidate because it was a frameshift variant in an established gene that is associated with a very closely matching phenotype to the patient. This variant has been previously reported in two homozygous recessive individuals with progressive pseudorheumatoid dysplasia (PPD) and was found to segregate with disease in one affected homozygous relative [1,2]. There are no loss of function homozygous WISP3 variants in The Exome Aggregation Consortium (ExAC) indicating that this is uncommon in an unaffected population.

This frameshift variant is predicted to alter the protein beginning at amino acid 265 with a premature termination codon 31 amino acid downstream. This premature termination codon occurs in the last exon and therefore may escape nonsense-mediated decay, resulting in a truncated protein. Importantly, several other truncating variants have been identified downstream of this position in individuals with PPD [2–4] and progressive pseudorheumatoid arthropathy of childhood (PPAC), indicating truncating variants in the last exon of *WISP3* are not tolerated in some cases. Accordingly, this variant met our criteria to be classified as likely pathogenic based upon co-segregation and the predicted impact of the variant, and the phenotype in the proband is most consistent with PPAC.

Segregation confirmation (PCR and Sanger sequencing) used samples from one affected sister and four unaffected siblings. The variant co-segregated with disease in the homozygous state in the affected sister and all unaffected siblings tested were heterozygous. A list of other variants and the disorder are in the supplementary data section on PPAC, available at *Rheumatology* Online.

Genomic sequencing identified the causal variant and identified an exact disorder, which was not previously established despite thorough investigation. There are substantial benefits to identifying a pathogenic variant in addition to diagnosis. While clinical management will not be substantially changed, the proband and affected cousin had been treated for JRA. This incorrect diagnosis could have been avoided by sequence analysis, a benefit considering the potential side effects. Now, biologics may also be ruled out of the treatment plan.

Unnecessary clinical screening of at-risk family members and the attendant uncertainties of diagnosis can also be avoided. The proband has three children (with a fourth child expected), all under surveillance for this disorder. These individuals may now be genotyped for this pathogenic variant to avoid unnecessary surveillance. In addition, if potential carriers enter a consanguineous marriage, testing is available to clarify recurrence risk and enable family planning.

Genomic sequencing is expected to become the prevalent sequencing technique for monogenic disorders, with a diagnostic rate in known disorders of 25–33%. Given sequencing costs approaching $1000, it may be cost effective to sequence complex cases of undetermined aetiology earlier in the diagnostic process. If the expected cost to reach a diagnosis and subsequent familial surveillance is >$3000–4000 (based on the positive predictive value of the test), it would be appropriate to sequence and pursue familial surveillance only in affected individuals. While the complexity and success rates may differ among disorder types (e.g. rheumatology, immunodeficiency or autoimmune polyinflammatory syndromes), these rates and costs will be measurable. Beyond healthcare savings, other benefits include a reduction in absenteeism and reduced uncertainty. We recommend this strategy particularly in consanguineous families (which may obviate the need for broad familial sequencing) in selected cases of atypical musculoskeletal symptoms of juvenile onset.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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Non-infective endocarditis with systemic embolization and recurrent stroke in systemic sclerosis

Rheumatology key message

- Non-bacterial thrombotic endocarditis with systemic embolization and stroke can occur in systemic sclerosis patients.

SIR, SSc is a rare, multisystem autoimmune disease, characterized by small vessel vasculopathy, autoimmunity and uncontrolled fibrogenesis. Patients are at risk of severe morbidity and mortality in cases of internal organ involvement with subsequent dysfunction and failure. Low-grade endocardial inflammation with valvular disease has been described but is considered a very rare phenomenon in SSc patients [1].

In 2013, a 27-year-old black female presented with a painful necrotic toe ulcer. Clinical examination demonstrated multiple digital ulcers on both hands and feet and skin fibrosis extending to the thorax and abdomen. Laboratory analysis revealed positive ANA, with the detection of anti-topoisomerase I antibodies. Capillaroscopy showed an early SSc pattern with multiple megacapillaries. Pulmonary function tests and high-resolution CT suggested early interstitial lung disease. The patient was diagnosed with rapidly progressive early dcSSc and treated with a calcium antagonist, MTX and i.v. prostaglandins for ulcer healing. Four months later the patient presented with a non-fluent aphasia and mild sensorimotor deficit. Intracerebral haemorrhage was excluded and i.v. recombinant tissue plasminogen activator was administered. On brain MRI, bihemispheric areas of diffusion restriction were documented (Fig. 1A and B). Cerebral MRI angiography showed reduced flow in a distal branch of the left middle cerebral artery without convincing evidence of vasculitis. Lumbar puncture was unremarkable. Transoesophageal echocardiography demonstrated a posterior mitral leaflet vegetation with concomitant valvular insufficiency (2/4), highly suggestive of endocarditis. This had not been identified on previous transthoracic echocardiography, nor on a recently performed cardiac MRI. Serial blood samples and cultures showed no signs of infection or inflammation. Anti-cardiolipin antibodies and lupus anticoagulant were absent.

After initial improvement, she suddenly developed a left hemiparesis with dysarthria. MRI showed new areas of ischaemia in the frontal and insular region in the right hemisphere with occlusion of an M2 branch (Fig. 1C and D). No other aetiologies for bilateral ischaemic insults were identified. The diagnosis of nonbacterial thrombotic endocarditis (NBTE) was made and treatment with low molecular weight heparin (LMWH) was initiated. At present, there is an incomplete recovery with persistent left hemiparesis.

We present the case of a non-bacterial thrombotic endocarditis with systemic embolization and recurrent stroke in a Mauritanian female with SSc. Recent evidence shows that SSc patients are at increased risk of ischaemic stroke, and this is suggested to reflect primary vascular involvement of the brain with obliterative vasculopathy, endothelial dysfunction and vasospasms, resulting in focal and diffuse hypoperfusion [2]. In our patient, there was no evidence of primary cerebral vascular involvement and the rapid recurrence of stroke in the contralateral hemisphere suggested an embolic mechanism. Myocardial and pericardial disease are frequently present in SSc patients, but endocardial involvement is considered an extremely rare event [1]. Although post-mortem studies have described endocardial vegetations in as many as 5 of 28 SSc patients [3], only a few case reports describe the presence of such vegetations in living patients. To our knowledge, there is only one case report suggesting systemic embolization from a mitral vegetation as the origin of multiple ischaemic lesions [4]. However, others challenged this case because of the presence of cryoglobulinaemia and severe anaemia.

The occurrence of this rare and severe complication in our patient might be related to her ethnic background, but this remains speculative [5]. With regard to therapy, there is no consensus in patients with non-bacterial thrombotic endocarditis. The most recent clinical practice guidelines on antithrombotic therapy and prevention recommend treatment with full-dose i.v. unfractionated heparin or with s.c. LMWH *vs* no anticoagulation in patients with NBTE and systemic or pulmonary emboli [6]. The indications and appropriate timing for surgery in non-infective endocarditis have not been formally studied and should be based on an individualized decision. Severe valvular dysfunction and recurrent embolic events despite anticoagulation are clear surgical