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Distinguishing between the innate immune response due to ocular inflammation and infection in a child with juvenile systemic granulomatous disease treated with anti-TNF-α monoclonal antibodies

Sirs, Early-onset sarcoidosis (EOS) is often diagnosed if there is granulomatous involvement of an organ or sometimes as a diagnosis of exclusion in a child presenting with fever, rash and swollen joints. Recent evidence points to the fact that EOS is synonymous with juvenile systemic granulomatous disease (JSGD), also eponymously known as Blau syndrome (BS) or Jabs disease [1, 2]. They share clinical features of uveitis, dermatitis and arthritis, and are caused by inherited (BS) or sporadic (EOS) mis-sense mutations in the NACHT (NAIP (neuronal apoptosis inhibitory protein), CIITA (MHC Class II transcription activator), HET-E (incompatibility locus protein from Podospora anserina) and TP1 (telomerase-associated protein) protein domain of the NOD2 (CARD15) gene, a major orchestrator during innate immune responses [1, 3].

Granulomatous disease of any origin may cause a panuveitis characterized by inflammation in the anterior and vitreous chambers and also the choroid or retina. We report a case of JSGD with a novel mutation and highlight the difficulty in distinguishing between granulomatous inflammation and infection in ocular inflammation. The importance of this is magnified when anti-TNF-α agents are implicated. We also speculate on mechanisms by which infection and inflammation may share a similar clinical profile.

A 15-month-old Caucasian male, C.P., presented with a 2-week history of spiking fevers, a follicular, erythematous rash and symmetrical polyarthritis affecting the small joints of hand, ankles, knees and wrists and hips (Fig. 1). He had normocytic anaemia (7 g/dl), normal ferritin and elevated ESR and CRP (100 mm; 200 mg/l). Autoantibodies including RF and ANA were negative and infection was excluded. Biopsies were not taken from skin or SF.

A clinical diagnosis of systemic-onset JIA was made initially followed by treatment with MTX, IVIG and anakinra alongside frequent, intermittent courses of oral, IA and i.v. CS therapy for recurrences of rash and arthritis over the next 4 years. Consequently, etanercept and MTX were instituted when C.P. was 6 years old. Etanercept was stopped upon developing bilateral anterior uveitis [4]. In order to control both ocular disease and arthritis, adalimumab was started but 8 weeks later, C.P. was admitted as an emergency with papilloedema, headache and raised CSF pressure, CSF leucocyte count and protein. Investigations for tuberculosis were negative including CSF PCR, CSF and blood culture, ELISpot™ (Mabtech, Nacka, Sweden) IFN-γ-release assay (IGRA) and TST (tuberculin skin test). Despite negative results, he was treated empirically with a full course of quadruple therapy for tuberculosis meningitis and adalimumab was stopped.

Ocular inflammation relapsed during anti-tuberculous therapy with reduction of vision attributable to panuveitis [4] with choroidal infiltrate; this responded to oral CS and MTX. Aqueous fluid was sampled under general anaesthetic for Mtb PCR but the sample volume was insufficient.

At this stage, we revised the differential to consider inflammatory granulomatous diseases as neither granulomatous ocular disease nor recurrent rash are consistent...
with a diagnosis of JIA. Venous blood samples from C.P. and his biological parents were obtained for genomic DNA extraction and genotyping of the NOD2 exonic regions. This analysis revealed a novel, de novo heterozygous mutation at position c.1558 C > T in exon 4 encoding the amino acid substitution H520Y in C.P., confirming a diagnosis of JSGD. Following reported success with infliximab and its more potent TNF-\(\alpha\) blockade, C.P. was restarted on infliximab after 9 months of anti-tuberculous therapy normal lung imaging and repeated negative ELISpot\textsuperscript{TM}. C.P. is now 8 years old, he remains in drug-induced remission for joint and ocular disease and has vision of 6/5 in both eyes.

Discussion

We believe our case of BS is amongst the few known cases in the UK and the first to report an encephalopathy although cranial neuropathies and seizures have been described [2]. However, concomitant tuberculous meningitis remains possible as false-negative CSF MTb PCR, TST and IGRA assays alongside failure to isolate the MTb organism do occur, partly due to reduced T-cell function in young children [5]. This, in addition to their immature dendritic cell population increases susceptibility to disseminated tuberculous disease during TNF-\(\alpha\) blockade [5].

Tuberculous inflammation and autoinflammation, such as BS in children or sarcoidosis in adults cause tissue/organ-specific granulomatous responses, including choroidal infiltrate in the eye. Ocular biopsy involves risk to sight, which contributes to the diagnostic and management challenges highlighted by this case. The discovery of a single gene, NOD2, as the cause of a widespread granulomatous response, suggests that an aberrant innate immune system could explain the clinical overlap in these diseases.

The innate immune system is a rapidly deployed, first response in host defence; its dysregulation causes autoinflammation [6]. Toll-like receptors (TLRs) or cytosolic nucleotide-binding oligomerization domain-like receptors (NLRs) including NOD2 detect specific pathogens [6]. For example, NOD2 recognizes a component of bacterial peptidoglycan cell walls, resulting in activation of an inflammasome and production of inflammatory cytokines including IL-1\(\beta\) [6].

Although the function of NOD2 mutations in JSGD is unclear, they do not appear to mediate their effect by an excess of IL1 [7]. It has been suggested that loss of function NOD2 gene mutations that occur in Crohn’s disease may cause reduced activity of NOD2, which in turn suppresses naturally occurring negative feedback on TLRs at the gut mucosal surface causing a granulomatous inflammatory response to commensal organisms [6, 8]. Thus, a microbial trigger in conjunction with a defective NOD2 signalling pathway might also result in a loss of negative regulation of TLRs on joint, uveal or retinal cells by remote pathogens [9]. For instance, mycobacterial components and Propionibacterium acnes have been implicated as a trigger for sarcoidosis [10].

Improved recognition of the spectrum of clinical phenotype, appropriate biopsy and mutation analysis will enhance the diagnosis of juvenile systemic granulomatous disease. From a broader perspective, the discovery of a gene that causes uveitis affords us the opportunity to understand the role of innate immunity in a variety of systemic diseases that affect the eye.

Rheumatology key message

- Distinguishing between non-infectious, granulomatous disease and TB affecting the eye is difficult, particularly in children.

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Potential biomarkers of monocyte/macrophage activity in a patient with sarcoidosis, treated with infliximab

Sir, sarcoidosis is a granulomatous disease of unknown, and probably heterogeneous, aetiology. The histological resemblance between lesions in sarcoid and mycobacterial infection suggests that some cases of sarcoidosis may be driven by unidentified intracellular bacteria [1]. Most patients can be managed with CSs and/or conventional immunosuppressants. However, TNF-α blockade has been proposed for patients whose disease is resistant to conventional strategies [2–5]. This therapy has proven efficacious only in a minority of steroid-resistant patients [6, 7], and presents the risk of reactivating latent microbial infection. There is, therefore, a need for biomarkers of efficacy of anti-TNFα therapy (or indeed other immunosuppressive therapies). Previous work has revealed peripheral blood monocyte hyperactivity in sarcoidosis [8]. Here, we report that several markers of monocyte hyperactivity rapidly normalized following successful anti-TNF-α therapy of steroid-resistant, advanced sarcoidosis.

Our patient was a 44-year-old Afro-Caribbean male who was considered to be in the terminal stages of multisytem sarcoidosis. As a retired United States Air Force serviceman, he had a history of exposure to beryllium, depleted uranium and hydrazine. He had presented with breathlessness 16 years earlier. Bilhar lymphadenopathy was noted on plain chest radiograph and a transbronchial biopsy revealed granulomatous inflammation consistent with sarcoidosis. His disease progressed despite CSs and AZA, to involve renal, rhinological and cutaneous sites; severe lung involvement necessitated use of a wheelchair and continuous domiciliary oxygen.

Investigations revealed a systemic inflammatory response (ESR: 75 mm/h; CRP: 33 mg/ml) but normal renal and liver function, serum angiotensin-converting enzyme and autoantibody titres. Sputum microscopy and culture, T-spot and beryllium function tests were negative. High-resolution CT of the chest revealed bilateral hilar lymphadenopathy (Fig. 1A, arrow), widespread ground glass and fibrosis (Fig. 1A). Due to his pulmonary compromise, lung function tests were impractical; he had a saturation of 92% (PaO2 10.3 kPa) on oxygen 4 l/min.<(36%) at rest and desaturated to 80% with exercise.

Following discussion of risks and benefits, our patient opted for a trial of infliximab 3 mg/kg/month and replacement of AZA with MMF 3 g/day. There was rapid subjective improvement and he was able to perform his first 6-min walk test (6MWT; Fig. 1B). Since the contributions of MMF and infliximab to this improvement were unclear, MMF alone was continued. A repeat 6MWT at 6 months revealed increased walk distance, decreased rest time and reduced desaturation (Fig. 1B). Unfortunately, this improvement was not sustained and our patient reported a return of his systemic symptoms. Therefore, we reintroduced...