CASE REPORT

Endogenous *Candida* endophthalmitis and osteomyelitis associated with CARD9 deficiencyNicholas Jones,¹ Tomaz Garcez,² William Newman,³ David Denning³¹Manchester Royal Eye Hospital, Manchester, UK²Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK³University of Manchester, Manchester, UK

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SUMMARY

A 25-year-old woman presented with unilateral red eye and visual blur, and was found to have panuveitis with an inflammatory white mass at the macula, initially presumed to be *Toxoplasma* retinitis. After failure to respond, she underwent vitrectomy, which produced *Candida albicans*. Despite intraocular and systemic antifungal treatment, she lost all vision in that eye. Two years later, she developed unilateral hip osteomyelitis leading to total hip replacement and also revealing *Candida* infection. By clinical exome sequencing, she was then found to have caspase recruitment domain 9 (CARD9) deficiency, an autosomal recessive disorder that causes a specific susceptibility to candidal infections. She remains otherwise well but on lifelong fluconazole prophylaxis.

BACKGROUND

Endogenous endophthalmitis is a rare but sight-threatening infection. Fungal endophthalmitis is most often seen following line infection in patients undergoing prolonged intravenous treatment, or in 'mainlining' drug addicts,¹ and sometimes in the immunodeficient. The importance of caspase recruitment domain 9 (CARD9) as a signaller in the *Candida* immune pathway has only recently been described,² and susceptibility to *Candida* infection may be caused by CARD9 gene mutations.³ *Candida* endophthalmitis associated with CARD9 deficiency has not previously been described; we report a case also associated with fungal osteomyelitis.

CASE PRESENTATION

A 25-year-old woman presented with a 5-day history of right (R) red eye and blurred vision. She was otherwise completely well with no significant medical history. On examination, the visual acuity was R 6/36, left 6/6. The left eye was completely normal. The right eye showed severe panuveitis (anterior chamber cells +++ with no hypopyon, severe vitritis) and a large white focal inflammatory mass at the R macula (figure 1). She was initially treated on the presumption of primary ocular toxoplasmosis, with cotrimoxazole and prednisolone, with which the uveitis improved significantly. She was, however, found to be seronegative for *Toxoplasma* (both IgM and IgG), *Borrelia* and *Bartonella*, and Mantoux and interferon- γ testing was negative. The ACE level was normal at 35. After tapering the prednisolone dose, the lesion and uveitis worsened (figure 2), and she underwent vitrectomy and internal limiting membrane (ILM)

peel, which revealed a choroidal/intraretinal mass that could not be removed; microscopy of vitreous revealed no organisms, and the sample was culture-negative (aerobic and anaerobic) at 10 days. Aqueous humour was PCR negative for herpes simplex virus types 1 and 2, varicella zoster virus and *Candida*.

Over the succeeding month, vision worsened and the patient developed an enlarging mass (figure 3) with vitreous involvement strongly suggestive of fungal infection (figure 4). On further questioning about risks of fungal infection, it transpired that the patient had undergone skin tattooing 4 months before presentation, and, prior to that, a tongue piercing. She had not injected drugs and there was no history of intravenous access. She began oral voriconazole and underwent further surgery including cataract extraction by phacoemulsification with intraocular lens (IOL) implantation, with epiretinal membrane peel, which was complicated by intraocular haemorrhage and retinal detachment requiring silicone oil injection. An intraocular sample was found to be PCR positive for *Candida* but negative for *Aspergillus*. Voriconazole 200 mg two times a day was continued for a further 8 weeks. Intraocular inflammation settled but the eye became phthisical with leukokoria and no perception of light.

OUTCOME AND FOLLOW-UP

Two years and 9 months after initial presentation with endophthalmitis, the patient developed progressive pain in the left hip; imaging revealing narrowing of the joint space and a subarticular cyst,

Figure 1 The right fundus at presentation, showing a white macular lesion with associated serous retinal elevation.

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Figure 2 An enlarged macular lesion with posterior vitreous infiltration after tapering of oral steroids.

progressing to destructive arthritis. Six months after developing symptoms, she underwent total hip replacement. The excised femoral head showed granulomatous osteomyelitis and synovitis with focal osteonecrosis, and fungal hyphae were present, *Candida albicans* being cultured from granulation tissue (*C. albicans* is a dimorphic yeast that may show either hyphae or yeast cells in tissue). There was no evidence of mycobacteria. *Candida* was also present in the vagina, and although there was no fungaemia, 1,3- β -D-glucan was present (>80 pg/mL), indicating systemic fungal infection. She was HIV-seronegative and there was no evidence of cellular immunodeficiency. She was treated with high-dose systemic antifungals, tapering to maintenance fluconazole, and remains well after a further 2½ years using fluconazole 100 mg daily, which is likely to be lifelong.

Clinical whole exome sequencing was undertaken. Genomic DNA was extracted, using standard methods, from a peripheral blood sample. Enrichment was achieved using SureSelect Human All Exon Kit v.5 (Agilent). Paired-end sequencing was run on an Illumina HiSeq2500. The sequence data were mapped to the human reference genome (UCSC Genome

Figure 3 A substantially enlarged lesion now covering the posterior pole.

Figure 4 Vitreous strands and 'pearls' suggesting fungal endophthalmitis.

Browser hg19) with the Burrows-Wheeler Aligner. Variant calling was performed with a modified Genome Analysis Toolkit (GATK) v.2.4.7 pipeline. A panel of six genes associated with increased susceptibility to fungal infection, including *CARD9*, was selected for detailed bioinformatic sequence analysis. Confirmation of variants determined by exome sequencing was undertaken by Sanger sequencing on an ABI 3730 DNA sequencer (Applied Biosystems).

The patient was identified to be compound heterozygote for two novel variants in *CARD9*. A missense variant c.1138G>C, p.(Ala380Pro) and a synonymous variant c.951G>A, p.(Arg317Arg). Neither variant was present in control databases (1000 Genomes, Exome Variant Server, Exome Aggregation Consortium) of over 70 000 individuals. The synonymous variant was inherited from her unaffected mother and is predicted to be pathogenic as it disrupts normal messenger RNA splicing. The missense variant arose de novo (absent in the mother or/and father), increasing the likelihood that this is the second pathogenic variant. This means that the risk to the patient's two siblings is negligible. *CARD9* deficiency is a recessive condition and therefore the risk to the patient's future offspring would be very low (dependent on the very low risk that her partner was a carrier for a pathogenic variant).

DISCUSSION

The immune response to *Candida* infections is complex and genetic systemic failures have been well-summarised;⁴ the initial stage requires recognition of the fungus by either toll-like receptors or dectin-1 (a pattern-recognition receptor for fungi); the latter requires the presence of *CARD9* within the antigen-presenting cell. This activates NACHT, LRR and PYD domains containing protein 3, which leads to the release of the cytokines interleukin 1 β (IL-1 β), IL-6 and IL-18, contributing to T-cell recruitment. *CARD9* also interacts with dectin-2, another C-type lectin, via a different signalling pathway that activates Th17 cells.⁵ *CARD9* is therefore a key component of the signalling pathway, and deficiency may contribute to both, mucosal and invasive candidiasis.

The importance of CARD9 in the immune response to *Candida* was first described by Gross *et al.*² and its role in T_H induction and IL-17 production, shortly thereafter.⁶ Deficiency of CARD9 has been described: in a large consanguineous family, 3 of 7 affected members died of invasive candidiasis;³ in 8 families, 17 members developed deep dermatophytosis, of whom 4 died;⁷ and in 5 offspring of consanguineous marriages, each developed invasive *Candida* meningoencephalitis or colitis.⁸

Nosocomial candidaemia is an important and potentially fatal complication, especially on intensive treatment units.⁹ *Candida* endophthalmitis is rare, causing only 0.7% of uveitis seen at this tertiary referral centre over a 24-year period,¹⁰ but *Candida* is the most frequent pathogen causing fungal endophthalmitis.¹¹ The great majority of patients are infected parenterally¹ and more than half of patients are immunocompromised.¹¹ Reports of endogenous *Candida* endophthalmitis in patients with no apparent predisposing risk are anecdotal,¹² but one case was reported arising soon after skin tattooing in a patient with asplenia.¹³ Outcomes are often poor with one-third of patients developing severe visual loss (Snellen worse than 6/60).¹⁴

Deficiency of CARD9 clearly facilitates invasive candidiasis and, if gaining intraocular access, is likely to cause aggressive endophthalmitis, as in our patient. We suggest that any patient

presenting with *Candida* endophthalmitis in the absence of a route of access and/or clear predisposing cause such as immunocompromised or diabetes, be assessed for potential immune abnormalities including CARD9 deficiency.

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Contributors NJ conceived the report. All the authors contributed significant clinical information and opinion. All the authors read and edited the manuscript.

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Learning points

- Remember the SPUR acronym to initiate investigations for immune deficiency: Severe, Persistent, Unusual or Recurrent infection.
- Invasive candidiasis in children and young adults without clear underlying causes requires evaluation for caspase recruitment domain 9 (CARD9) deficiency.
- Exome sequencing is an efficient and cost-effective means of identifying rare inherited conditions.
- Patients found to be CARD9 deficient should use prophylactic fluconazole 100 mg/day to reduce the risk of further invasive candidiasis.

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