APID2016 CASE SUMMARY: ADULT ONSET CGD

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Case: A mosaic of suspicious infections

A 66 year-old gentleman presented with *Serratia marcescens* urosepsis on a background of distant *Burkholderia cepacia* urosepsis and disseminated *Nocardia transvalensis* infection. There was no family history suggestive of primary immune deficiency.

Neutrophil oxidative burst testing (by DHR-flow cytometric method) was significantly abnormal and, on first impressions, consistent with X-linked CGD. However, a small (6%) population of neutrophils appeared to burst normally. Genetic sequencing of the CYBB gene identified a novel missense mutation that was predicted to result in a functionally deficient protein. The patient was treated as having Chronic Granulomatous disease (CGD) with prophylactic antibiotic therapy and interferon gamma.

Adult-onset CGD is seldom described in the literature. A PubMed literature search revealed six published cases. Of these six, 4 patients presented in their 20s and 2 presented in their 60s. All cases involved mutations of the CYBB gene, in particular splice sites. 2 patients were females with evidence of skewed lyonisation.

The patient’s daughter came to the attention of our clinical team due to concerns of propagation of the X-linked CYBB mutation. However, the patient’s daughter had a normal DHR-NOB and did not have the CYBB mutation identified in her father. The patient’s daughter was quite confident of paternity and this was confirmed by further formal genetic analysis.

The absence of the mutation in the patient’s daughter and his attenuated phenotype with a residual population of functionally normal neutrophils led to the conclusion that the patient demonstrated somatic mosaicism at the CYBB locus.

Mosaicism is defined as the presence of two or more cellular populations with distinct genotypes in one individual. Mosaicism is more common in males and with increasing age. The genetic size of mosaicism may be variable and thus, in some instances, it may not be detected by low resolution cytogenetic/genetic analysis (i.e karyotyping, microarrays). Unsurprisingly, mosaicism is associated with malignancy, particularly haematologic.

Mosaicism has been described in one case of adult-onset CGD (Wolach et al, 2005). This female patient began to develop typical infections at the age of 66. Analysis revealed a mosaic CYBB mutation and skewing of X-inactivation toward the CYBB-mutant neutrophil population.

Our patient remained well on prophylactic therapies until approximately 2 years after his diagnosis. He was diagnosed with minimally-differentiated Acute Myeloid Leukaemia and passed away soon after. Whilst there is no established relationship between CGD and acute myeloid leukaemia, as mentioned above there is an association with mosaicism.

This case demonstrates that CGD should be considered as a diagnosis in adult patients who present with infections with organisms that are highly associated with this primary immune deficiency. Furthermore, the demonstration of CYBB mosaicism raises the possibility that mosaicism at other loci may be an important cause of adult-onset immune deficiency.
Reference: