Letters to the Editors

Delayed reactivation of chronic infantile neurologic, cutaneous, articular syndrome (CINCA) in a patient with somatic mosaicism of CIAS1/NLRP3 gene after withdrawal of anti-IL-1 beta therapy

Sirs,

Chronic infantile neurologic cutaneous and articular (CINCA) syndrome is a rare, early-onset autoinflammatory disorder and the most severe form of cryopyrin-associated periodic syndrome (CAPS) (1, 2). This condition is associated with mutations in the *NLRP3* gene that encodes NALP3, a key component of the inflammasome complex regulating IL-1β production. A conventional genetic analysis fails to detect disease-causing mutations in 40% of patients (3); somatic mosaicism for *NLRP3* mutations has been identified in 69% of patients without germline mutations (4-6). The pathogenic role of IL-1 in CAPS has been demonstrated by the achievement of complete response after treatment with the anti-IL1 biologic agents (7).

We report the case of 20-year-old girl who was diagnosed with CINCA syndrome at the age of two. She presented since birth with episodic fever and persistent urticarial erythematous rash. Laboratory data consistently showed leukocytosis, increased inflammatory indexes, serum amyloid A, immunoglobulins and hypochromic microcytic anaemia. Later on, she presented hepatosplenomegaly and lymphadenopathy, arthritis of the left hip and of the left knee, bilateral oedema of the optic disc, and swelling of the proximal left tibia, consistent with chondroid dysostosis at bone biopsy.

CINCA syndrome diagnosis was then formalised (8). Conventional mutation analysis of CIAS1 gene did not find any mutation; a somatic mutations in exon 3 of CIAS1 was detected (c1298 C>T mutation was found with a 3.2% allelic frequency).

Treatment with anakinra, IL-1β receptor antagonist, was immediately started, achieving complete remission as well as the recovery of the tibial lesion. Five years later, treatment with anakinra was switched to canakinumab, a human monoclonal anti-human interleukin-1β antibody (150 mg/kg/dose every 8 weeks).

Ten years after starting anti–IL-1β treatment, we decided to increase the interval between the canakinumab administrations (150 mg every 12 weeks, for three times), and she showed no flares. Considering that the mosaicism affects only a very low percentage of the cells, we decided to withdraw therapy. She remained healthy for about one year, and then the disease slowly relapsed. Initially she presented urticarial rash, diffuse arthralgia, asthenia and headache; then papilloedema reappeared. Blood tests showed an increased in inflammatory markers and serum amyloid A. Canakinumab was started again with rapid and complete clinical and laboratoristic response after two injections.

This is the first report of withdrawal of anti-IL1β therapy in a patient with CINCA disease after a long lasting complete remission. The delayed and slow relapse of symptoms after the suspension of treatment has no clear explanation. Indeed, it could be expectable a recurrence of symptoms soon after the wash out of the drug from the body, which takes 2–3 months. We can hypothesise that the longer duration of remission after withdrawal of treatment could be due to the switch off self-amplification vicious typical circles of CAPS (6). In fact, it has recently been proven that inflammatory particles released by macrophages undergoing pyroptosis (ASC specks) can propagate and amplify inflammation with a prionoid behaviour also in non-mutant NLRP3 cells (9).

This is probably due to the mosaic mutation present in few cells that can lead to so severe and complete phenotype. Prolonged anti-inflammatory treatment with IL-1 blocker could interrupt the cascade of self-activation of the system. Starting from just few diseased cells in subjects with somatic mutations, it may take a long time to fuel again the propagation of inflammation and to sustain the systemic disease. Thus, although subjects with somatic mosaicism for NLRP3 mutations can have similar severity of diseases compared with patients with germline mutation, they may require less frequent treatment, once the complete remission is reached with IL-1 blockers. The study of serum levels of ASC specks can help understanding of this phenomenon. The rapid response to the resumption of therapy emphasise, once more, the effectiveness of anti IL1 and the importance of therapy in keeping off the inflammation, improving of the prognosis and preventing of the most feared complication of the disease, such as amyloidosis.

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Competing interests: none declared.

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