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LETTER TO EDITOR

Autoinflammation with Infantile Enterocolitis Associated with Recurrent Perianal Abscesses

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To the Editor

The NOD-like receptor family CARD domain containing 4 (NLRC4) gene was initially described in 2001; however, it is only since 2014 that its mutations, mostly heterozygous gain-of-function mutations with complete penetrance, have been associated with distinct syndromes and diseases, known as NLRC4 inflammasomopathies [1]. They are characterized from recurrent episodes of autoinflammation due to hyperactivation and spontaneous formation of the NLRC4 inflammasome, a large multimolecular cytosolic complex that mediates, through caspase-1, the proteolytic cleavage of immature pro-IL-1β and pro-IL-18 to their mature biologically active forms and a programmed inflammatory cell death process known as pyroptosis [1]. Until now, three NLRC4 inflammasomopathy phenotypes have been described in a total of 37 cases: autoinflammation with infantile enterocolitis (AIFEC) in 10 cases, familial cold autoinflammatory syndrome 4 (FCAS4) in 26 cases belonging to only two families, and neonatal-onset multisystem inflammatory disease (NOMID) in 1 case [1–3]. Given the rarity of the disease and the diversity of clinical presentation, we report the case of a boy with NLRC4 inflammasomopathy presenting with AIFEC syndrome. This report focuses on some new appearing symptoms and differences from previously reported patients, namely AIFEC-associated perirectal abscesses and milk protein allergy.

A male Caucasian full-term neonate, born to non-consanguineous parents and with no allergies, presented at 20 days of age with bloody diarrhea, dehydration, weight loss (− 1 Kg from birthweight), respiratory distress, abdominal distension, hypothermia, and metabolic acidosis (pH 7.11, HCO_3 4.1 mmol/L). The boy was fed since birth with breastmilk and formula. Routine laboratory investigations showed leukocytosis (WBC 24×10^9/L), increased serum C-reactive protein (CRP, 82 mg/L, normal < 10 mg/L) and procalcitonin levels (16 ng/mL, normal < 0.5 ng/mL), hypertransaminasaemia (AST 89 IU/L, normal < 45 IU/L), thrombocytopenia (platelets 18×10^9/L), coagulopathy (prothrombin time 21.6 s, fibrinogen 74 mg/dL, d-dimers 1.4 μg/mL), hyperferritinemia (1,680 μg/L, normal range 10–150 μg/L), and decreased glomerular filtration rate (14 mL/min/1.73 m^2). Blood, urine, CSF, and stool cultures did not reveal any microorganism. The baby was mechanically ventilated for 24 h, treated with intravenous fluids, inotropes, and antibiotics for suspected sepsis and transfused with fresh frozen plasma, packed red blood cells, and platelets. After recovery, he was fed with an elemental formula, due to food intolerance, in combination with total parenteral nutrition. Serum immunotrypsinogen, fecal trypsin, and a chloride sweat test for cystic fibrosis, were all normal. Abdominal ultrasonography was normal too, apart from mild hepatosplenomegaly. No abnormal findings were observed macroscopically on gastroscopy and colonoscopy; histology showed moderate chronic inflammation (Fig. 1a) and eosinophilic infiltration of the duodenum (Fig. 1b), mild eosinophilic infiltration of the esophagus, gastric mucosa and rectum, and mild-to-moderate chronic rectal inflammation.

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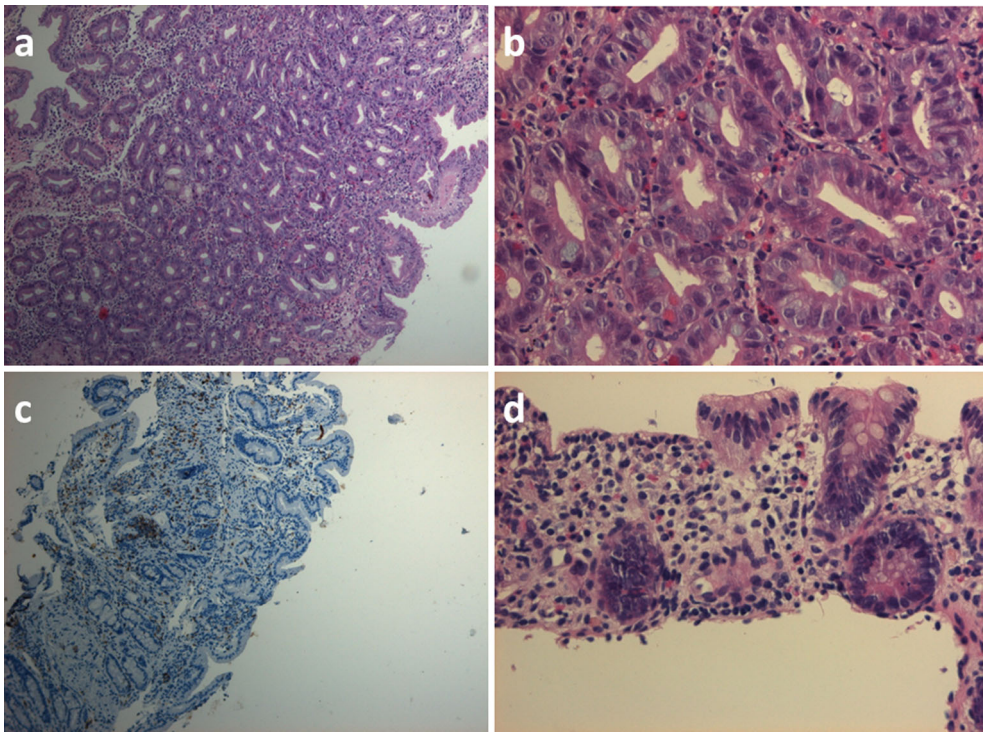

Fig. 1 **a** Inflammatory infiltrate and **b** increase of eosinophils in duodenum (H&E staining); **c** mild villous atrophy in duodenum (CD3 immunostain); **d** moderate chronic inflammation of lamina propria in colon with an increase of eosinophils (H&E staining)

During the next 6 months, the infant presented 11 episodes of recurrent fever (Fig. 2); there was no rash or any other features of autoinflammation. The first five episodes were accompanied with clinical signs of systemic inflammatory response and increased markers of inflammation, but no cytopenias; again, all cultures were sterile. Between flares, the baby was well appearing; biomarkers of infection, as well as blood biochemistry, including serum triglycerides and ferritin levels, were all normal apart from intermittent peripheral eosinophilia (eosinophils 0.2–2.7 × 10^9/L). During the following six episodes, the infant appeared mildly affected, but not septic; markers of inflammation were within normal range. However, the last 4 flares were accompanied by recurrent perianal abscesses emerging at different sites around the anus (Fig. 3); treatment with antibiotics was followed by partial remission. No fistulas were detected on a pelvic magnetic resonance imaging. A repeat gastrointestinal endoscopy at the 7th month of age showed a nodular appearance of mucosa

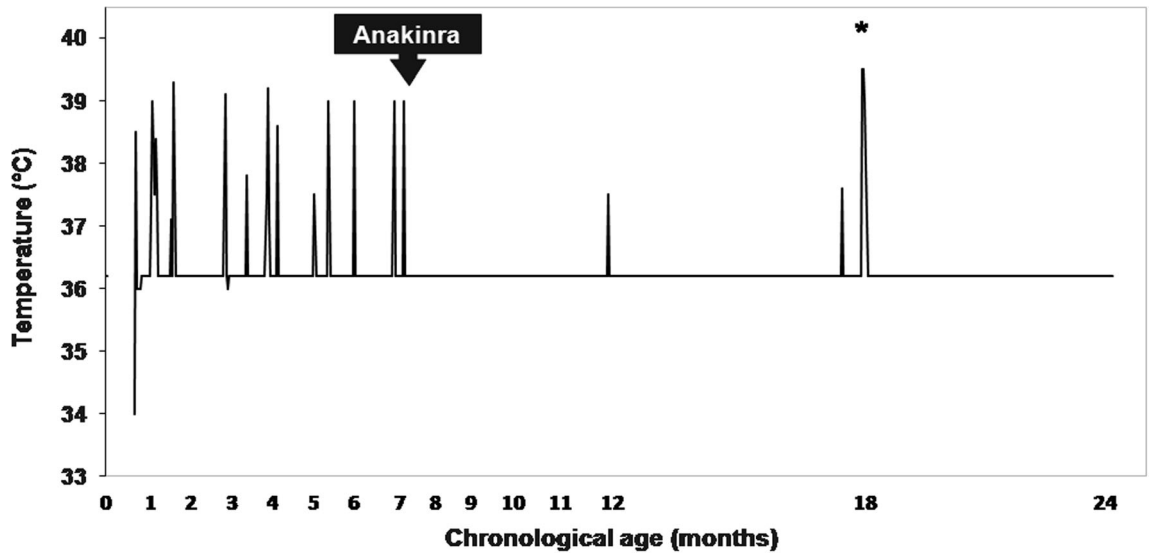

Fig. 2 Flare frequency, duration, and max temperature before and after anakinra treatment in our patient. *This febrile episode was attributed to roseola infantum infection

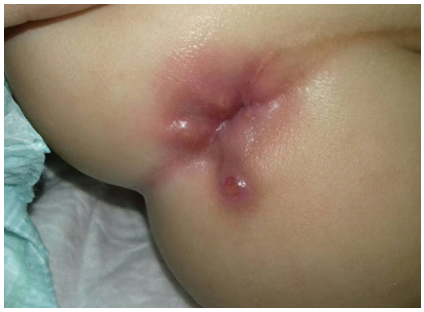

Fig. 3 Perianal abscesses

in the rectum and sigmoid colon. On histology, mild esophagitis, non-specific chronic gastritis, chronic duodenal inflammation with a moderate increase of eosinophils, mild/moderate atrophy of villi (Fig. 1c), and moderate/severe chronic inflammation of colon with a moderate/severe increase of eosinophils and presence of multiple lymphoid follicles (Fig. 1d) were observed.

On an extensive immunologic workup, serum levels of IgG, IgA, IgM, C_3, C_4, and CH50, were within normal values, whereas IgE levels were increased (up to 364 IU/mL, normal < 29 IU/mL). Cow's milk protein-specific IgE concentrations increased from class 0 at neonatal age to class 3 at the 4th month of age and remained elevated despite feeding with an elemental formula. Normal for age percentages and absolute numbers of B, T, and NK cells and subpopulations were noted on lymphocyte immunophenotyping in peripheral blood. CD3+CD4+CD25+FOXP3 cells, Tregs and Th17 cells, neutrophil oxidative burst, IRAK4/NF-kB signaling, LPS-induced IL-10 production, and integrin expression on leukocytes were all normal. Serum IL-1β, IL-6, and TNF-α levels determined between flares were within normal range, whereas IL-18 concentrations determined in two separate serum samples were significantly elevated (35,876 pg/mL and 35,289 pg/mL, respectively, normal < 358 pg/mL). Serum amyloid-A levels were mildly increased (23 mg/L, normal up to 10 mg/L); IgD levels ranged from 3 to 5 mg/dL (normal 0.3–1.2 mg/dL). Endocrine and metabolic workup, urine mevalonic acid, cardiologic and ophthalmological evaluations, hearing tests, and a bone marrow biopsy showed normal findings. No mutations were detected for Familial Mediterranean Fever or hyper IgD syndrome. Whole-exome sequencing analysis demonstrated a heterozygous *NLRC4*c.1022T>C (p.Val341Ala) de novo mutation, thus confirming the diagnosis of autoinflammation with infantile enterocolitis (AIFEC).

Therapy with an IL-1 receptor antagonist (anakinra, 2 mg/Kg/day, SC) was initiated at 7 months of age, followed by remission of flares (Fig. 2). Besides, perianal abscess recurrences were eliminated in number and severity; they presented a short course with spontaneous remission within 1 to 2 days. At 2 years of age, our patient is on anakinra; he is still on a diet free of cow's milk protein as an oral challenge test with formula was followed by diarrhea. He has the regular schedule of vaccinations apart from the live ones. His anthropometric measurements and neurodevelopment are appropriate for age. Despite his good clinical course, serum IL-18 concentrations remain significantly elevated (41,931 pg/mL).

Only ten cases with AIFEC syndrome have been reported worldwide in the literature so far; four of them (with three belonging to the same family) shared an identical to our patient's gain-of-function mutation (p.Val341Ala) on the NLRC4 gene; in one case, an alternate substitution (c.1021G>C, p.Val341Leu) was identified, two cases were described with a mutation in the leucine-rich repeat (LRR) domain of NLRC4 (c.G1965C/p.W655C), whereas the remaining three cases harbored unique mutations (T337S, T337N, and S171F) [1–3]. In all cases, including our patient, the initial symptoms were consistent with systemic inflammatory response accompanied by enterocolitis; features of macrophage activation syndrome (MAS) were also recorded. MAS risk in AIFEC cases has recently been attributed to chronic (sometimes lifelong) elevation (> 40× normal) of mature IL-18 derived entirely from intestinal epithelia [4]. This fact potentially explains the phenotype of these patients as opposed to that typically seen in other inflammasomopathies, i.e., Familial Mediterranean Fever/FMF and cryopyrin-Associated periodic syndromes (CAPS) caused by activating mutations in MEFV/PYRIN and NLRP3 gene respectively, which are not associated with MAS. In both the NLRP3 and MEFV inflammasomopathies, despite profound inflammasome activation, there is minimal/modest and less consistently IL-18 elevation; lower expression of NLRP3 and MEFV than NlRC4 in intestinal epithelial cells has also been noted [4].

In a few AIFEC cases, an event that could act as triggering factor was reported such as an upper respiratory infection, a minor operation (circumcision), and emotional stress [1]. In our patient, it could be hypothesized that cow's milk protein allergy led to intestinal damage that triggered the NLRC4 auto-activation. Alternatively, enterocolitis in the context of AIFEC syndrome might have provoked disturbances of the gastrointestinal mucosal barrier leading to susceptibility to cow's milk protein allergy persisting into infancy [5].

Recurrent perianal abscesses, which are for the first time reported in a patient with NLRC4 inflammasomopathy, may constitute a prodromal feature of inflammatory bowel disease (IBD). A number of primary defects in innate immunity may lead to IBD/IBD-like pathology [6, 7]; of them, X-linked inhibitor of apoptosis protein deficiency, mutations in the genes encoding IL-10 and its receptor, and chronic granulomatous disease, typically cause severe perianal inflammation, often accompanied by fistula [6]. Genetic associations between Crohn's disease and carriage of polymorphisms within the *NOD2* gene, a member of NLRs have also been described [7]. Furthermore, elevated expression of the inflammasome-related cytokines IL-18 and IL-1β in the intestinal mucosa of patients with IBD has been reported [7].

The very high serum levels of IL-18 in our patient, before and after anakinra treatment, confirm previous reports showing that IL-18 concentrations are chronically elevated in these patients [1]. In the context of the extremely elevated IL-18 levels, we wonder whether clinical remission in our patient could be fully attributed to anakinra treatment and/or to the natural evolution of the disease; remission of symptoms has been reported in AIFEC cases after the first year of life, even without treatment [1]. Thus, discontinuation of anakinra in due course and treatment with an IL-18 antagonist, in case of recurrence of symptoms, is under consideration.

In conclusion, we presented the case of an infant with a de novo mutation (p.Val341AIa) within the NLRC4 gene and a clinical picture consisted of AIFEC syndrome. The patient shared common features with the previously reported patients, but also presented differences and novel clinical manifestations, these of recurrent perianal abscesses and milk protein allergy. Close observation and follow-up of the reported cases, including our patient, may reveal new aspects of AIFEC syndrome and possible connections to other autoinflammatory diseases and IBD.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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