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CROHN'S DISEASE WITH PROMINENT FEVER, HOMOZYGOUS R202Q MEFV VARIANT AND GOOD RESPONSE TO COLCHICINE: A CASE REPORT AND REVIEW OF LITERATURE.

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ABSTRACT

We describe the case of a young woman with high intermittent fever as the prominent manifestation of an underlying Crohn's disease. Genetic investigations revealed the presence of R202Q variant of the Familial Mediterranean Fever gene (MEFV), which plays a key role in regulating the inflammasome biology and in the control of systemic inflammation. The patient had a good clinical response after administration of colchicine, a known regulator of the inflammasome, suggesting a direct involvement of R202Q as a disease modifier in Crohn's disease and a possible role for colchicine in the control of Crohn-related systemic inflammation.

INTRODUCTION

Crohn's disease (CD) is a common, though frequently elusive, cause of intestinal and systemic inflammation and a known cause of fever of unknown origin (FUO) [1-2]. The pathogenesis of CD is currently thought to involve an intricate network of interactions between multiple genes and the complex non-sterile environment of the gut [3]. Anomalies in the inflammasome compartment are emerging players in such scenario. The Familial Mediterranean Fever gene (MEFV) encodes for pyrin, a protein known for its striking regulatory role towards the inflammasome. Specific mutations in the MEFV gene have been associated with Familial Mediterranean Fever (FMF), while other gene variants are emerging as disease modifiers in CD [4]. Since ancient times colchicine has been widely used for its antinflammatory properties, due to inhibition of the microtubules and interference with the biology of the inflammasomes. Colchicine proved efficacious for the tratment of Crohn-associated pyoderma gangrenosum [5] and secondary amyloidosis [6-8], while less is known about its possible applications in the setting of Crohn-related systemic inflammatory symptoms [9].

CASE PRESENTATION

A 20-year-old woman complained for a persisting intermittent daily fever. The febrile crisis occurred suddenly with intense chilling, usually in the second half of the day and peaked even at 41°C before rapidly terminating with profuse sweating. High dose corticosteroids prevented the recurrence of the febrile episodes, while antibiotics were not effective.

Extensive clinical, laboratory (**Table 1**) and imaging studies (including total body CT-scan and brain MRI), performed during the first three months from the beginning of the fever only revealed a marked hypersedimetry (ESR = 98 mm/h, normal 0-15 mm/h) and CRP elevation (CRP = 4.24 mg/l, normal 0-0.5mg/l), but no organ involvement other than a genital herpetic reactivation due to intensive corticosteroid therapy. Given the absence of evident clinical signs, the responsiveness of the fever to corticosteroids, the absence of any microbial growth at repeated cultural tests and the negative serology for HIV, HBV, HCV, CMV, Salmonella typhi, S. parathyphi, Brucella, Toxoplasma, Leishmania, Rickettsiae, Borrelia, Bartonella, Plasmodium spp. as well as the negative interferon response to a challenge with tubercular antigens, most infectious aetiologies were excluded. Similarly, clinical data and unremarkable laboratory tests (including ANA, ADNA, anti-ENA, ANCA, AMA, ASMA, anti-transglutaminase antibodies) were not suggestive for the most common autoimmune diagnoses. In particular a diagnosis of Adult-Onset Still's disease was rejected because of the absence of significant neutrophilia, hyperferritinemia, LDH or transaminase elevation and the lack of clinically relevant lymphadenopathy or arthritis. A bone marrow biopsy was normal and no hidden lesions were detected at imaging studies, thus driving to the exclusion of occult abscesses or neoplasias.

At admission to our Unit the patient had a normal heart rate, blood pressure, oxygen saturation and respiratory rate; body temperature was 36.5°C; thoraco-abdominal examination was normal with the exception of a mild dull pain in the left inferior abdominal quadrant. Skin examination was unremarkable. In the afternoon of the first day after admission the patient become febrile with a body temperature of 40°C. This pattern occurred repeatedly during next days. Moreover, since the patient

still complained for left lower quadrant abdominal pain, an abdominal ultrasonography was performed, which revealed the thickening of the wall of the last ileal loop. The subsequent colonoscopy showed an area of inflammation and mucosal atrophy at the level of the last ileal loop and multiple biopsies were performed. Histopathology revealed the presence of multiple foci of chronic inflammation, highly suggestive for CD. The diagnosis of CD was further supported by the presence of anterior bilateral uveitis at fundoscopic examination and by the positivity of anti-Saccharomyces cerevisiae antibodies (ASCA). Meanwhile genetic investigations revealed homozygosity for R202Q variant of the MEFV gene. For purposes of corticosteroid sparing the patient was given 2 mg/day colchicine, with good control of the febrile crisis in three days.

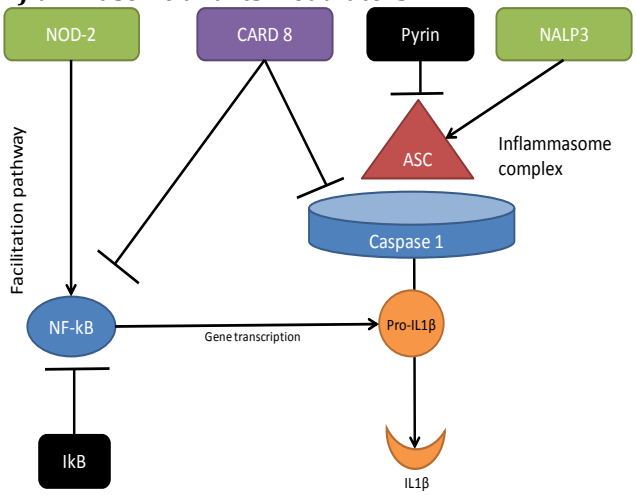
Table 1

	Value observed	**Reference range**
White blood cells/mm^3	5,200	4,800-10,800
Haemoglobin (g/dl)	12.7	14-18
Platelets/mm^3	256,000	130-400
AST (U/l)	32	5-41
ALT (U/l)	23	6-55
LDH (U/l)	218	125-220
GGT (U/l)	20	11-50
ALP (U/l)	119	53-128
ESR (mm/h)	98	1-15
C-reactive protein (mg/l)	4.24	0-0.5
Serum creatinine (mg/dl)	0.6	0.5-1.1
Ferritin (ng/ml)	228	30-400
ANA (Anti Nuclear Antibodies)	Negative	Negative or <1:80
Anti Cardiolipin IgG and IgM Antibodies	Negative	Negative
AMA (Anti Mitochondrial Antibodies)	Negative	Negative
ASMA (Anti Smooth Muscle Antibodies)	Negative	Negative
ANCA (Anti Neutrophil Cytoplasm Antibodies	Negative	Negative
Anti-transglutaminase IgA antibodies	Negative	Negative
Rheumatoid factor	Negative	Negative
Anti-EBV IgG antibodies	Positive	Negative
Anti-EBV IgM antibodies	Negative	Negative
Serum Hepatitis B S Antigen (HBsAg)	Negative	Negative
Anti-CMV, HIV, HCV, Salmonella typhi, S. parathyphi, Brucella, Toxoplasma, Leishmania spp., Rickettsia spp., Borrelia, Bartonella, Plasmodium spp, Treponema pallidum, Leptospira spp. antibodies	Negative	Negative
Interferon response to tubercular antigens	Negative	Negative
Bone Marrow Biopsy	"Normal, no evidence of neoplastic infiltration"	NA

DISCUSSION

We described the case of a patient with homozygous R202Q variant of the MEFV gene, who developed CD with prominent high-grade fever and good response to colchicine. Colchicine is known for its efficacy in many autoinflammatory diseases like FMF and gout [10]. Such conditions share an increased activation of the inflammasome compartment as a common pathogenic feature [11]. An inflammasome complex (e.g. the NALP3-inflammasome) usually assemblies around an innate pattern recognition receptor (mainly of the NOD-like receptor family) [11]. When challenged by different danger associated molecular patterns (DAMPs), the pattern recognition receptor (PRR) is able to recruit caspase 1 either directly (if it contains a caspase activation and recruitment domain: CARD) or through the mediation of a apoptosis speck protein (ASC) [11]. In the NALP3-inflammasome, which is the target of pyrin, caspase 1 ultimately acts by processing IL1β to its active form. This reaction is facilitated by a NOD-2/NFkB-dependent increase in the inflammasome substrate (i.e. pro-IL1β) and it is triggered by the innate PRR NALP3, which in turn recruits caspase 1, through the mediation of an ASC [11] (**Figure 1**). Other intracellular factors, such as IkB, CARD8 or pyrin act as counter-regulators. Dysfunctional engagement and activation of innate immune receptors (NOD-2, NALP3) lead to impaired IL1β-response against intestinal bacteria, chronic "frustrated" inflammation and possibly CD susceptibility, due to insufficient NFkB-dependent facilitation [12] and NALP3-dependent triggering [13]. By contrast (according to the syncretistic view exposed by Roberts et al. in their recent article [14]) gain of function mutations of NALP3 could as well confer susceptibility to CD by means of excessive enhancement of the inflammasome function, when associated to impaired braking of the inflammasome machinery (e.g. loss of function mutations of CARD8 [15]; **Table 2**).

Figure 1 : schematic representation of the NALP3 inflammasome and its modulators



The NALP3 inflammasome assemblies around an innate pattern recognition receptor (NALP3 or cryopyrin), which in turn recruits caspase 1 through the mediation of a apoptosis speck protein (ASC). Caspase 1 processes pro-IL1β to its secretive and bioactive form (IL1β). A primary increase in the expression of pro-IL1β due NF-kB signaling takes places in parallel, when NOD-2 innate receptors are challenged with bacterial muramyl dipeptides. IkB and CARD8 act as counter-regulator of NF-kB and reduce the availability of substrates for the inflammasome machinery. CARD8 could also interact directly with the inflammasome. Transcription of the MEFV gene leads to the production of pyrin, which regulates the activation of the inflammasome by competition with NALP3 for ASC.

Similarly to CARD8, pyrin counter-regulates the activation of the inflammasome (**Figure 1**) and its gene-determined functional impairment is responsible for the development of FMF. Moreover selective mutations in the MEFV gene have been recognized as disease modifiers in

CD [4]. According to Fidder et al. M649V, V726A and E148Q mutations would confer susceptibility to the development of stricturing complications as well as extraintestinal manifestations of CD. No association was proven towards inflammatory symptoms. A single case report of a pediatric patient documented an association between homozygosity for M649V, refractory CD with high-grade fever and dramatic response to colchicine [9]. By contrast homozygous R202Q variant of the MEFV seems to occur more frequently in FMF patients [16], although larger studies are required to define its precise role in this disease [17]. On the other hand an association between R202Q and susceptibility to the development of CD has been excluded by a large multicenter study [18]. However much less is known about the role of R202Q mutation (and especially R202Q homozygosity) in modulating the clinical phenotype of CD.

The association we have observed between homozygous R202Q and CD with prominent febrile manifestations seems to suggest that in our patient this mutation could have drifted the disease course towards systemic inflammation. Larger studies are required to confirm this hypothesis. Additionally the patient had a good clinical response after colchicine administration. This finding agrees with previous reports, describing the efficacy of this drug in the treatment of Crohn-associated pyoderma gangrenosum [5], secondary amyloidosis [6-8] and fever [9]. Direct interaction with the inflammasome machinery [10] is just one of the possible ways by which colchicine could modulate local and systemic inflammation in CD. A limitation the virulence of CD-specific bacterial strains by impairment of the cytoskeleton [19] could also maybe be advocated to explain these sporadic evidences. Further research in this field would possibly disclose novel pathogenic insights and therapeutic fallouts in CD and other diseases with autoinflammatory features.

Table 2

Mutation	*Predicted cellular phenotype (see also ref. [4] and [14])*	*Predicted effect on CD phenotype*
NOD-2 loss	Defective recognition of bacteria → impaired host response → chronic inflammation	↑ susceptibility
NALP3 gain	Enhanced caspase1 activity under normal pro-IL1β expression, if mutation is isolated → more efficient clearance of bacteria	Protective
CARD 8 loss	Enhanced NF-kB response (↑pro IL1β), but no increase in the inflammasome response if mutation is isolated	Protective
+ NOD2 loss	Possible compensation for reduced recognition of bacteria	Susceptibility not affected
+ NALP3 gain	Increased facilitation (NF-kB) and triggering (NALP3) of IL1β production → increased autoinflammation	↑ susceptibility
+ NALP3 loss	Impaired inflammasome response under continuous substrate (pro-IL1β) production → chronic inflammation	Susceptibility not affected or slightly increased
MEFV - M649V, V726A and E148Q	Reduced braking on NALP3 inflammasome → facilitated autoinflammation	Stricturing pattern and extraintestinal manifestations
MEFV - R202Q	Reduced braking on NALP3 inflammasome → facilitated autoinflammation	*unknown*

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