

Autoinflammatory Diseases: Mimics of Autoimmunity or Part of its Spectrum? Case Presentation

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Received: 9 January 2008 / Accepted: 16 January 2008
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Abstract

Introduction: Autoinflammatory diseases are very rare diseases presenting within a wide clinical spectrum. Recognition of the main clinical features are challenging due to overlapping or mimicking with autoimmune diseases.

Discussion: A case series is reviewed to illustrate typical and atypical features and the difficulties of these diagnoses in the low prevalence areas—a typical unrecognized case of familial Mediterranean fever (FMF) in a youngster, an atypical adult case with overlapping of FMF with Behçet disease, and an early presentation of FMF in infant presenting with inflammatory colitis, as well as the overlapping features within the cryopyrin diseases spectrum in an 8-year-old boy who presented with systemic onset arthritis.

Conclusion: These cases may represent examples of a very puzzling relationship among disorders of innate and adaptive immune systems and inflammation.

Keywords Autoinflammatory disorders · Muckle–Wells syndrome · CINCA/NOMID syndrome · familial Mediterranean fever

Introduction

The main challenge of addressing this topic, during the symposium, was to provide a possible liaison of immuno-

deficiency and autoimmunity, in the context of clinical features of autoinflammatory disorders.

The current definition of autoinflammatory disorders covers a wide spectrum of seemingly unprovoked inflammation that occurs independent of the adaptative immune system, with systemic inflammation in many organs and systems. Great contribution to understanding the common pathways and mediators of apoptosis, inflammation, and cytokine signaling has been stressed in the article by Gattorno et al. [1] in this issue.

The study of autoinflammatory diseases has progressed in the last few years from the clinical characterization of the various disorders to the genetic analysis and to the definition of the functional defects involved in the regulation of inflammatory response. The growing knowledge of the different syndromes reveals groups of well-characterized clinical, genetic, and functional entities, but there are still a lot of questions to be answered, and once again, the clinical data may be of great importance, showing superposition of manifestations of various diseases or exhibiting unusual characteristics that will lead to the investigation of the underlying mechanisms involved which represent important contribution to a better understanding of the conditions associated with chronic inflammation.

The four cases that will be present were seen at a time when the role of the genes and encoded proteins were beginning to emerge, and they were examined retrospectively, fitting into the algorithm proposed by Samuels and Ozen, 2006 [2], to step guidance for genetic testing, in doubtful cases.

Familial Mediterranean Fever

Case 1 This is a case of a 19-year-old young man, from Italian ancestry, without family history. Since his early childhood, he was a very irritable boy. At the age of 12 years,

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he presented the first episode of severe interscapular pain and after that these episodes became frequent, with 1 to 3 days of duration, and almost always associated with upper respiratory tract infection and fever. He was seen by many different physicians without a diagnosis. Investigations during attacks disclosed elevated acute phase reactants [ESR: 94 mm/hour CRP: 92 mg% and an ANA of 1/80 (documented in two different crisis)]. The pulmonary investigation (sliced CT) disclosed a doubtful pleural thickening at the pain region. The MEFV mutation screening showed heterozygous for the E148Q mutation. After the introduction of colchicine, only two attacks were documented precipitated by viral infections.

The important observation about this case is related to the fact that long-standing painful febrile diseases, especially in mild forms, in adults can be a challenge for most of the doctors. According to the proposed algorithm [2], to make the diagnosis of these patients even more challenging after excluding occult infections, and malignancies, as well as more common autoimmune diseases such as systemic juvenile idiopathic arthritis or systemic lupus erythematosus, the clinician still need to consider less common syndromes that lack clear mendelian pattern.

In the specific case of familial Mediterranean fever (FMF), physicians are encouraged to treat these cases on clinical grounds based on family history, clinical history including age at onset, frequency, and duration of the attacks, physical exams, and nongenetic laboratory tests.

Should genetic testing be reserved for more ambiguous cases? If the family history and ethnic background are difficult to obtain, and the logistic and financial constraints preclude genetic testing, alternatively, one should submit the patient to colchicine trial to prevent organ damage associated with amyloidosis, especially when other effective therapy are now available (rHuIL-1RA).

Case 2 This is a case of a 44-year-old female, from Armenian ancestry (both parents), who was referred to the hospital for gastrointestinal bleeding, fever, anemia (hemoglobin: 6.0 g/dl), and asthenia. The colonoscopic biopsy disclosed vasculitis and unspecific perivascular infiltrates. Her past history, in the last 3 years, included chest pain and pleuritis (X-ray and CT scan), aphtae, and painful genital ulcers. Her mother has FMF diagnosed in childhood, and one of her three daughters has a vasculitic syndrome, which started at 13 years of age, characterized by a sudden loss of audition, arthritis, and a persistent biopsy-proven vasculitic papular skin lesions in arms and legs.

The only alterations of her laboratory tests were a persistent elevation of acute phase reactants (ESR ranging from 48 to 82 mm/h), high platelet counts, and persistent anemia (Hb range: 6–11 g/dl). The ophthalmologic exam-

ination was normal, and screening for MEFV mutation indicated V726A heterozygous.

She started on colchicine and sulphasalazine, and her evolution was characterized by episodic sub-febrile attacks (37.5–38°C) and myalgias. After a year, she underwent a hysterectomy for myoma, and the exploration of abdominal cavity revealed abdominal adenomegaly and chronic peritonitis.

The remarkable points of this case were the absence of prior diagnosis of FMF, the disease presentation as a vasculitic syndrome compatible with the diagnosis of Behçet disease and, very puzzling, is the small-vessel vasculitic syndrome of her daughter.

Case 2 is an example of overlapping between FMF and Behçet disease. Rabinovich et al, 2007 [3] performed MEFV analysis for the three most common mutations (M694V, V726A, and E148Q) in 54 patients with Behçet disease and found a significantly higher frequency than expected for ethnically matched healthy individuals. They suggested that MEFV might act as a susceptibility and modifier gene in Behçet disease. However, Koné-Paut et al., 2007 [4] analyzed mevalonate kinase (MVK), cold-induced autoinflammatory syndrome 1 (CIAS1), and proline/serine/threonine phosphatase-interacting protein 1 (PSTPIP1) genes in 97 patients with Behçet disease, and 51 matched healthy controls could not demonstrate any significant increases in MVK, CIAS1 or PSTPIP1 mutations in patients with Behçet disease compared to controls. Imirzalioglu et al, 2005 [5] also screened 42 Behçet disease patients and 66 healthy controls for common MEFV gene mutations (E148Q, M680I, M694V, and V726A) with evidence of higher mutation rates in patients than in healthy controls, suggesting that the MEFV gene may be involved in the pathogenesis of Behçet disease.

Case 3 This is a case of a 14-month-old female from Ashkenazi Jewish ancestry, parents with second-degree consanguinity and with an older healthy brother. She had chronic diarrhea since 10 months of age and 2- to 3-day attacks of periodic spiking fever, accompanied by abdominal pain. Initial diagnosis of lactose intolerance or inflammatory bowel disease was suspected. Her initial laboratory tests were all normal except for the increase of acute phase reactants: CRP-12 mg %, ESR-82 mm/h. An intestinal biopsy revealed unspecific inflammation in sigmoid and lymphonodular hyperplasia. The MEFV mutation screening showed M680 heterozygous and M694V heterozygous mutations. Colchicine was started, and in the next 2 years, only mild episodes of fever associated with upper respiratory tract infections were observed.

To examine possible association between ulcerative colitis and MEFV genes, Giaglis S et al., 2006 [6]

investigated 25 first-diagnosed and untreated patients compared to 28 rheumatoid arthritis patients, and 65 healthy controls, for mutational screening of exons 10 and 2 of MEFV gene, with increased frequency of MEFV mutations in ulcerative colitis patients, especially in those with episodic arthritis. This suggests a possible modifying effect of MEFV in the disease process and its localization within the joint. Sari S et al. 2007 [7] reported the concurrent manifestation of infantile ulcerative colitis and FMF in three infants of less than 6 months of age. In two patients, the disease could not be controlled until colchicine was added to the drug regimen. They suggest the infantile ulcerative colitis should prompt the search for MEFV mutations, as it may influence the disease management.

Cryopirin Disease

Case 4 This is a case of a boy first seen at age of 8 years old as a systemic juvenile idiopathic arthritis because of polyarthritis, fever, and rash since 8 months. He evolved into persistent polyarthritis with multiple exostosis, recurrent attacks of spiking fever every 3–4 months with 10-day duration, highly positive inflammatory markers during attacks and recurrent otitis and deafness. He also had a diffuse uveitis with retinal vasculitis. His phenotype with

dysmorphic osteocartilagenous exostosis in the knees as well as the skin rash, uveitis, and deafness make his diagnosis unequivocal for CINCA syndrome, now recognized as a cryopirin disease (Fig. 1). After 1 year of follow-up, he presented pleuropericarditis, anemia, (hemoglobin 5.4 g/dl), generalized edema, hematuria, leucocyturia, proteinuria (0.9 g/24 h), low albumin (2.76 g/l), low C3, positive Waller Rose test for RF 1:128, negative ANA. Skin and synovial biopsy showed unspecific inflammatory process, without granulomas the renal biopsy disclosed a mesangial proliferative glomerulonephritis. In the next 7 years he maintained the skin rash with progressive knee arthropathy (Fig. 2). After several attempted treatment with high-dose prednisone, methotrexate and azathioprine and cyclophosphamide, with persistent fever attacks and several hospital admissions with uncontrolled disease, he evolved into heart failure and deceased at age 16. His autopsy findings were lung aspiration accompanied by chronic fibrotic meningitis, severe end-stage amyloidosis. Amyloid deposits were found in the kidneys, heart, spleen, thyroid, adrenals, gastrointestinal tract, skin, testis, and tongue.

The diagnosis of CINCA syndrome was established based in the phenotypes described in early days by Ansell et al. [8], Prieur et al. [9], and Yarom et al. [10]. In the search of earlier descriptions, a portrait by Thomas Brayne, a surgeon from Bradbury in England, made this phenotype unequivocal

Fig. 1 Typical clinical features of a cryopirin disease: craniofacial disproportion, knee arthritis and urticarial rash

Craniofacial disproportion



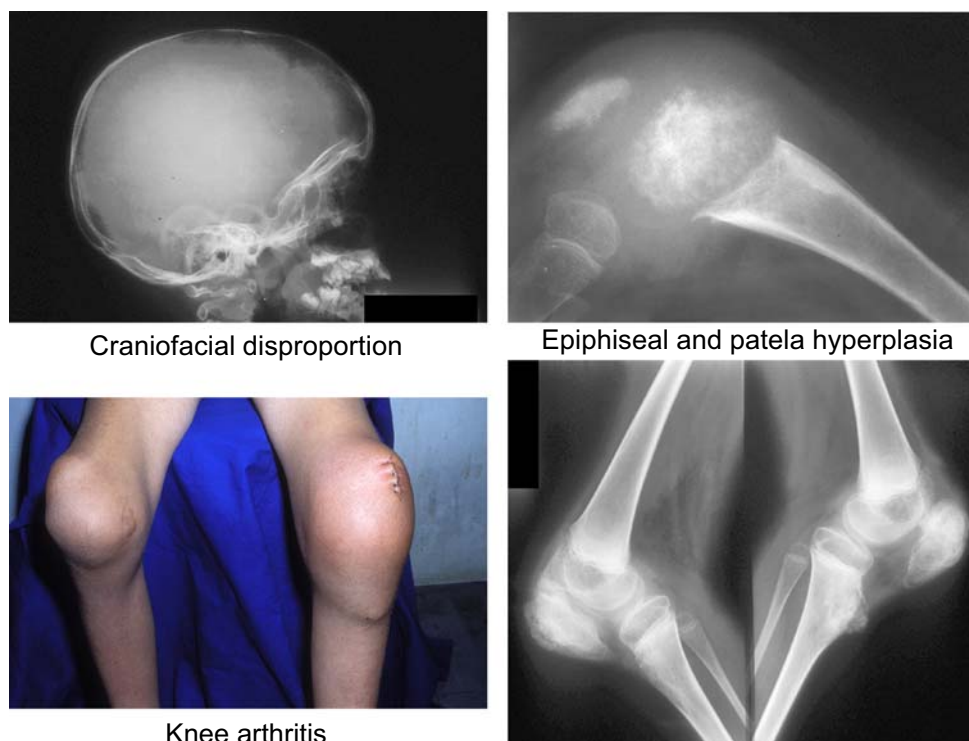
Knee arthritis



Urticarial rash



Fig. 2 Cryopyrin disease: craniofacial disproportion, typical bone overgrowth with epiphyseal and patella hyperplasia



(Travers and Allen, 2006 [11]). We also noticed overlapping features in their presentation. The puzzling aspect of this case was the glomerulonephritis and the presence of rheumatoid factor. The interesting feature was the kidney involvement earlier in the disease course. These features, kidney involvement, extension, and severity of amyloidosis, were more frequently described in association with Muckle–Wells syndrome, even though genetics testing has not been performed by the time, as the case was seen many years before the gene identification [12].

Overlapping features of CINCA and Muckle–Wells syndrome were reported in a French family described by Hentgen V et al, 2005 [13] as an intrafamilial overlapping clinical phenotype of CINCA and MWS, caused by a mutation in CIAS1 gene.

Hawkins et al. 2004 [14] reviewed the clinical features of three members of a family, all of whom had clinical characteristics of MWS associated with the CIAS1 variant V200M. However, additional features were identified, including exacerbation of their disease by cold and neurologic manifestations, described in FCAS and CINCA, respectively. The authors concluded that clinical features of the various syndromes associated with mutations in the CIAS1 gene may overlap to a greater extent than it has previously been recognized.

Arostegui et al, 2004 [15] investigated the involvement of the CIAS1 gene in seven unrelated Spanish families in whom a clinical diagnosis of CAPS was suspected. The previously unreported mutation and the incomplete pene-

trance found in two families expand the genetic basis underlying these autoinflammatory syndromes. These findings pointed to the possible genetic basis of these conditions, even in the absence of a family history.

Aksentijevich I et al, 2007 [16] tested the presence of CIAS1 mutations in 22 patients with CINCA, 12 with MWS, 18 with FCAS, and three probands with MWS/FCAS and found that a significant number of patients who are clinically diagnosed as having cryopyrinopathies do not have identifiable disease-associated mutations. Lequerré T et al. 2007 [17] described four generations and eleven members of a family with cryopyrin disease including the joint destruction description associated with a CIAS1-gene mutation. Four of these family members developed different combinations of CAPS manifestations, during childhood or adolescence. Sequencing of six family members' CIAS1-gene exon 3 identified a heterozygous mutation, c.1043C>T. Interestingly, this cryopyrin disease is distinct from CINCA syndrome and Muckle–Wells syndrome (MWS), which also result from exon 3 mutations in this gene. This is a previously unreported form of CAPS with atypical neurological signs, joint destruction, and livedo. This observation extends the clinical spectrum associated with CIAS1 mutations.

We examined also recent cases reported in the literature for overlapping features within the spectrum of autoinflammatory diseases, beyond the cases reported in this session. Interestingly, chronic noninfectious inflammation of the bone is a clinical feature of both chronic recurrent multifocal osteomyelitis and to a lesser degree querubism. Murine

models of both diseases have demonstrated that the bone inflammation is mediated by hematopoietic-derived cells and can occur in the absence of a functioning adapted immune system with the bones as inflammatory target [18].

Chronic recurrent multifocal osteomyelitis may be a subphenotype in individuals with SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis) and it can evolve into classic spondyloarthropathy suggesting they may be part of the same disease spectrum. Disease associations included palmar–plantar pustulosis (PPP), psoriasis vulgaris, and inflammatory bowel disease which suggested that an inflammatory pathway common to skin, bone, and gut is dysregulated in these disorders [19, 20, 21, 22].

Among the more recent descriptions of the endless spectrum of autoinflammatory disorders, another recently reported overlap was described in a 4-year-old TRAPS with myocardiopathy and sacro-ileitis not previously reported [23]. In addition, we found a case report of granulomatous nephritis associated R334Q mutation in NOD2, broadening the clinical spectrum of Blau's syndrome [24].

Ferrero-Miliani et al, 2007 [25] made a very important review of the pathways involved in chronic inflammation based on the knowledge that the pattern recognition molecules (PRMs) represent a diverse collection of molecules responsible for sensing danger signals, and together with other immune components, they are involved in the first line of defence. NALP3 and NOD2 belong to a cytosolic subgroup of PRMs. Nod-like-receptors (NLRs) have been associated recently with inflammatory diseases, specifically Crohn's disease, Blau syndrome (NOD2), FCAS, MWS, and CINCA/NOMID syndrome (NALP3). The exact effects of the defective proteins are not fully understood, but activation of nuclear factor (NF)-kappaB, transcription, production, and secretion of interleukin (IL)-1beta and activation of the inflammasome are some of the processes that might hold clues to the better understanding of these pathologies and their interrelation.

The puzzle has still many gaps to fill in. Recent discoveries regarding genetic and immunologic bases of autoinflammatory diseases have helped us to understand the role of the innate immune system in chronic inflammation and may help even further our understanding of inflammation-mediated bone resorption, a process seen in many rheumatic diseases.

References

- Gattorno M, Federici S, Pelagatti MA et al. Diagnosis and management of autoinflammatory diseases in childhood. *J Clin Immunol Suppl* 2008 (in press).
- Samuels J, Ozen S. Familial Mediterranean fever and other autoinflammatory syndromes: evaluation of the patient with recurrent fever. *Curr Opin Rheumatol* 2006;18:108–17.
- Rabinovich E, Shinar Y, Leiba M, Ehrenfeld M, Langevitz P, Livneh A. Common FMF alleles may predispose to development of Behçet's disease with increased risk for venous thrombosis. *Scand J Rheumatol* 2007;36:48–52.
- Koné-Paut I, Sanchez E, Le Quellec A, Manna R, Touitou I. Autoinflammatory gene mutations in Behçet's disease. *Ann Rheum Dis* 2007;66:832–4.
- Imirzalioglu N, Dursun A, Tastan B, Soysal Y, Yakicier MC. MEFV gene is a probable susceptibility gene for Behçet's disease. *Scand J Rheumatol* 2005;34:56–8.
- Giaglis S, Mimidis K, Papadopoulos V, Thomopoulos K, Sidiropoulos P, Rafail S, Nikolopoulou V, Fragouli E, Kartalis G, Tzioufas A, Boumpas D, Ritis K. Increased frequency of mutations in the gene responsible for familial Mediterranean fever (MEFV) in a cohort of patients with ulcerative colitis: evidence for a potential disease-modifying effect? *Dig Dis Sci* 2006;51:687–92.
- Sari S, Egritas O, Dalgic B. The familial Mediterranean fever (MEFV) gene may be a modifier factor of inflammatory bowel disease in infancy. *Eur J Pediatr*. 2007 May 23 [Epub ahead of print].
- Ansell BM, Bywaters EGL, Elderkin FM. Familial arthropathy with rash, uveitis and mental retardation. *Proc Royal Soc Med* 1975;68:24–5.
- Prieur AM, Griscelli C. Arthropathy with rash, chronic meningitis, eye lesions, and mental retardation. *J Pediatr* 1981;99:79–83.
- Yarom A, Rennebohm RM, Levinson JE. Infantile multisystem inflammatory disease: a specific syndrome? *J Pediatr* 1985;106(3):390–6.
- Travers R, Allen R. Chronic infantile neurological cutaneous and articular syndrome—an early description. *J Rheumatol* 2006;33: 822–4.
- Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. *Nat Genet* 2001;29:301–5. Nov.
- Hentgen V, Despert V, Leprêtre AC, Cuisset L, Chevrant-Breton J, Jégo P, Chalès G, Gall EL, Delpech M, Grateau G. Intrafamilial variable phenotypic expression of a CIAS1 mutation: from Muckle-Wells to chronic infantile neurological cutaneous and articular syndrome. *J Rheumatol*. 2005;32(4):747–51.
- Hawkins PN, Lachmann HJ, Aganna E, McDermott MF. Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. *Arthritis Rheum* 2004;50:607–12.
- Aróstegui JI, Aldea A, Modesto C, Rua MJ, Argüelles F, González-Enseñat MA, Ramos E, Rius J, Plaza S, Vives J, Yagüe J. Clinical and genetic heterogeneity among Spanish patients with recurrent autoinflammatory syndromes associated with the CIAS1/PYPAF1/NALP3 gene. *Arthritis Rheum* 2004;50:4045–50.
- Aksentijevich I, D Putnam C, Remmers EF, Mueller JL, Le J, Kolodner RD, Moak Z, Chuang M, Austin F, Goldbach-Mansky R, Hoffman HM, Kastner DL. The clinical continuum of cryopyrinopathies: novel CIAS1 mutations in North American patients and a new cryopyrin model. *Arthritis Rheum* 2007;56(4):1273–85.
- Lequerré T, Vittecoq O, Saugier-Verber P, Goldenberg A, Patoz P, Frébourg T, Le Loët X. A cryopyrin-associated periodic syndrome with joint destruction. *Rheumatology (Oxford)* 2007;46(4):709–14.
- Ferguson PJ, El-Shanti HI. Autoinflammatory bone disorders. *Curr Opin Rheumatol* 2007;19:492–8.
- Bergdahl K, Björkstén B, Gustavson KH, et al. Pustulosis palmoplantaris and its relation to chronic recurrent multifocal osteomyelitis. *Dermatologica* 1979;159:37–45.
- Bognar M, Blake W, Agudelo C. Chronic recurrent multifocal osteomyelitis associated with Crohn's Disease. *Am J Med Sci* 1998;315:133–5.
- Vittecoq O, Said LA, Michot C, et al. Evolution of chronic recurrent multifocal osteitis toward spondyloarthropathy over the long term. *Arthritis Rheum* 2006;55:665–9.

22. Rohekar G, Inman RD. Conundrums in nosology: synovitis, acne, pustulosis, hyperostosis and osteitis syndrome and spondylarthritis. *Arthritis Rheum* 2006;55:665–9.
23. Trost S, Rosé CD. Myocarditis and sacroileitis: two previously unrecognized manifestations of tumor necrosis factor receptor associated periodic syndrome. *J Rheumatol* 2005;32:175–7.
24. Meiorin SM, Espada G, Costa CE, et al. Granulomatous nephritis associated with R334Q mutation in NOD2. *J Rheumatol* 2007;34:1945–7.
25. Ferrero-Miliani L, Nielsen OH, Andersen PS, Girardin SE. Chronic inflammation: importance of NOD2 and NALP3 in interleukin-1beta generation. *Clin Exp Immunol* 2007;147(2):227–35.