Familial aggregation of Crohn’s disease and necrotizing sarcoid-like granulomatous disease

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Abstract
Granulomatous inflammatory diseases are disorders of an undetermined etiology, affecting different organs and having a diverse clinical course. Familial aggregation of these disorders is being reported increasingly, most commonly familial Crohn’s disease. We described the coexistence of Crohn’s disease and necrotizing sarcoid-like granulomatous disease in two siblings from a first-degree consanguineous Saudi family. The first child presented with recurrent abdominal pain associated with bloody stool and arthritis, whereas the second child presented with fever of unknown origin and lymphadenopathy as well as hepatomegaly without gastrointestinal tract disease. They are phenotypically different; however, they share a novel risk locus and allele. This report supports the heritability and familial aggregation of granulomatous inflammatory diseases and suggests that one causal mutation underlies both Crohn’s disease and necrotizing sarcoid-like granulomatous disease.

Keywords: Familial aggregation, granulomatous, inflammatory diseases, Crohn’s disease, sarcoidosis.

Introduction
Granulomatous inflammatory diseases are characterized by multisystem involvement and non-caseating epithelioid and giant cell granulomas formation. Crohn’s disease and sarcoidosis are among the spectrum of granulomatous inflammatory diseases. Clinical manifestations in both diseases are generally insidious with a progressive course and an unpredictable duration (1). Moreover, an overlap in the clinical features may be considerable depending on the initial presentation that may lead to a delay in diagnosis and consequent management (2). Diagnosis of granulomatous inflammatory diseases depends on clinical and laboratory findings confirming inflammation and more important histopathologic findings illustrating non-infectious granulomatous lesions.

Both Crohn’s disease and sarcoidosis are sporadic multifactorial disorders; nevertheless, Crohn’s disease tends to cluster in families but with an unclear inheritance pattern. Moreover, familial aggregation of early onset sarcoidosis is being described. Several reports proposing an affected family member is a significant recurrence risk factor for these diseases. A variety of genetic environmental factors may play a role in causing Crohn’s disease and sarcoidosis. Furthermore, increasing evidence suggests a common genetic basis in both entities (3-4).

We describe a family where Crohn’s disease and necrotizing sarcoid-like granulomatous disease have affected different siblings; they are phenotypically different but they share a novel risk locus and allele. This report supports the heritability and familial aggregation of granulomatous inflammatory diseases.

Case Presentations
A first-degree consanguineous Saudi family with five children was included in this study; three of them are healthy, whereas two siblings are affected with different granulomatous inflammatory diseases (Table 1). We described the detailed clinical data with a summary of molecular genetic results, which have been reported previously (5).

Case 1
A 10-year-old Saudi girl with a 4-year history of recurrent knee and wrist arthritis also had a history of fever and recurrent abdominal pain associated with bleeding per rectum but without a change in bowel habit. She was observed and evaluated in different hospitals; she was found to have a white blood cell (WBC) count of 16x10⁹/L (normal range 5-11x10⁹/L) and a platelet count of 679x10⁹/L (normal range 150-435x10⁹/L) as well as erythrocyte sedimentation rate (ESR) of 56 mm/h (normal range <15 mm/h). She underwent upper and...
lower gastrointestinal endoscopy; there was mild ulceration, and histopathology showed mild non-specific inflammation. Accordingly, she was treated with prednisone (1mg/kg/day). Her abdominal symptoms improved but she continued to have arthritis. Thus, she was administered naproxen, prednisone, and methotrexate treatment; however, she showed partial improvement.

She presented with bilateral knee and wrist arthritis on arrival at our hospital. Other physical examination including eye assessment was unremarkable. Our initial impression was juvenile idiopathic arthritis versus Crohn’s disease. Laboratory findings revealed WBC of 9.5×10^9/L with normal differential counts, hemoglobin level of 99 g/L (normal range 110-150 g/L) with hypochromic microcytic features, platelet count of 553×10^9/L, and ESR of 16 mm/h. Auto-antibodies findings showed antinuclear antibodies in the ratio of 1:80 (normal range <1:40), antineutrophil cytoplasmic antibodies (P-ANCA) 7.3 U/mL (0-6 U/mL), C-ANCA 7.2 U/mL (normal range <10 U/mL), and rheumatoid factor 13.8 IU/mL (normal range <14 IU/mL). Angiotensin converting enzyme (ACE) was 32 U/L (normal range <52 U/L). Renal and liver function and electrolytes were normal. Knee X-ray showed enlarged epiphysis with effusion, whereas hand X-ray revealed soft tissue swelling around the wrist joint. There were no erosive or destructive changes.

During tapering treatment, her symptoms recurred with bloody diarrhea; repeated lower gastrointestinal endoscopy showed multiple ulcerations. Histopathology examination ascertains chronic active ileitis and colitis with scattered mucosal non-caseating granulomatous lesions (Figure 1). All infectious causes including mycobacterial were negative.

We confirmed the diagnosis of Crohn’s disease. Therefore, she started on prednisone (1mg/kg/day), methotrexate (12.5 mg/week), and adalimumab 20 mg every 2 weeks. Fortunately, she showed progressive improvement and no relapse was observed after prednisone was discontinued.

**Case 2**

A 4-year-old girl, who was the sister of patient 1, presented with a 6-month history of recurrent fever. She was found to have hepatomegaly with elevated liver enzymes, alanine aminotransferase (ALT) level of 125 U/L (normal range <33 U/L) and aspartate transaminase (AST) level of 210 U/L (normal range <32 U/L), Gamma-glutamyl transferase (GGT) level of 115 IU/L (normal range 7-32 IU/L), and albumin level of 23 g/L (normal range 39-49 g/L). All infectious workup was inconclusive. However, she had WBC of 19×10^9/L, platelet counts of 735×10^9/L, and ESR of 48 mm/h. Bone marrow aspiration and biopsy showed hypercellular marrow without abnormal cells. Abdominal ultrasound showed para-aortic lymphadenopathy and hepatic nodular lesions, which was more prominent at porta hepatitis. Histopathology of liver biopsy revealed necrotizing granulomatous inflammation (Figure 2). Acid-fast bacilli (AFB) stain was negative in tissue culture, and nucleic acid amplification test using strand displacement amplification was also negative for AFB. The final report of tissue culture including mycobacterial and fungal infections was negative. She had elevated ACE (109 U/L) with normal serum immunoglobulin levels, T- and B-lymphocytes markers, and a normal oxidative burst assay. Thus, she was diagnosed with necrotizing sarcoid-like granulomatous disease and was treated with prednisone (1mg/kg/day); she showed a good response.

Whole-exome sequencing was performed as previously described (5). Briefly, a missense variant in GAL3ST2 (NM_022134.2; c.197C>T; p. Thr66Met), a major mucin sulfotransferase in the intestine, was identified in the homozygous state in both affected children but not in their unaffected siblings. The two variants are
extremely successful in identifying potential genes. Genome-wide association studies have been ex-
in patients with early onset sarcoidosis (7, 8).
inflammatory disease and were later discovered autosomal dominant inherited granulomatous causative mutations in NOD2 were found in the mechanism of cellular apoptosis. The same mutations may impact the regulatory have found to trigger granuloma formation.

Figure 2. Histopathology of liver biopsy revealed granulomatous inflammation with central necrosis and giant cells

Discussion

Childhood Crohn’s disease and early onset sarcoidosis are both inflammatory disorders, which share clinical similarity in the form of arthritis, cutaneous, and ocular manifestations. However, gastrointestinal involvement is an essential manifestation in Crohn’s disease, whereas sarcoidosis rarely affects the intestines.

Like other inflammatory diseases, the pathogenesis of Crohn’s disease and sarcoidosis is not yet entirely understood. However, it is believed to involve environmental triggers and genetic risk factors in genetically predisposed individuals (6).

Susceptible loci on the long arm of chromosome 16q12 have been identified in patients with Crohn’s disease. Mutations of caspase recruitment domains (CARD 15), which are nucleotide-binding oligomerization domain 2 (NOD2) and stretch of leucine rich repeats (IRR), have found to trigger granuloma formation. These mutations may impact the regulatory mechanism of cellular apoptosis. The same causative mutations in NOD2 were found in the autosomal dominant inherited granulomatous inflammatory disease and were later discovered in patients with early onset sarcoidosis (7, 8).

Genome-wide association studies have been extremely successful in identifying potential genes with numerous risk alleles of diverse rare diseases in different populations. For example, causal variants in multiple genes had been suspected to play a role in Crohn’s disease pathogenesis. The recurrence risk rate of developing inflammatory granulomatous disease is elevated among relatives of sarcoidosis patients compared with that in control subjects (9). Furthermore, few reports showed concurrent Crohn’s disease and sarcoidosis in the same patients, which were either idiopathic in origin or medication related. However, familial aggregation of Crohn’s disease and sarcoidosis in different members of the same family is rarely seen (10). Bambery et al described the coexistence of Crohn’s disease and sarcoidosis in different adult patients (n=8) from two Indian non consanguineous families. Unfortunately, there was no molecular genetic testing performed (10). We described a first-degree consanguineous family, where Crohn’s disease and necrotizing sarcoid-like granulomatous disease have affected different siblings. Nevertheless, they shared the same missense variant in GAL3ST2. Furthermore, a major mucin sulfotransferase was identified in the homozygous state in both of the affected children but not in their unaffected siblings; this result was compared and found absent in the databases of Saudi variants and controls (5).

Our findings support that Crohn’s disease and sarcoidosis are among the spectrum of granulomatous inflammatory diseases. Both require a high index of suspicion to reach the diagnosis in proper time. Clearly, the phenotype differences have an impact on the treatment and prognosis. This report emphasizes familial clustering of granulomatous inflammatory diseases and suggests that one causal mutation underlies both Crohn’s disease and necrotizing sarcoid-like granulomatous disease in this family.

References