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Case Report
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Hereditary and Pathogenetic Consequences of Sarcoidosis, Ulcerative Colitis, And Papillary Thyroid Carcinoma

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Abstract

Sarcoidosis is a systemic non-caseating granulomatous disease that can affect any organ including the lungs. lymph nodes, skin, and eyes most frequently. Sarcoidosis may occasionally be associated with other autoimmune or malignant disorders that share a common genetic background. We report an unusual case of two siblings presenting with a spectrum of multisystemic sarcoidosis, including pulmonary, ocular, renal involvement with simultaneous existence of ulcerative colitis and thyroid papillary carcinoma. Genetic analysis revealed identical HLA-DRB1*01:03 alleles suggesting a mutual genetic predisposition. The common identical HLA-DRB1 gene allele profile implies a familial link in susceptibility to sarcoidosis, the autoimmune and the malignant disorders of these patients. This case report reveals a common genetic background for three disorders with completely distinct pathologic backgrounds enlightening the role of genetic and hereditary factors in the pathogenesis of these conditions. The diagnostic challenges and the strategies for sarcoidosis associated with malignant and autoimmune disorders sharing a similar pathogenetic and a congruent genetic profile are also discussed. The presence of identical HLA-DRB1 alleles is the genetic hyperlink for the simultaneous occurrence of irrelevant diseases with completely distinctive mechanisms. The primary aim is to determine the role of genetic implications in the development of sarcoidosis with the accompanying autoimmune and malignant diseases to emphasize the need for further research.

Keywords: Sarcoidosis, Ulcerative colitis, Papillary thyroid carcinoma, HLA-DRB1.

Introduction

Sarcoidosis is a systemic granulomatous disease of unknown etiology, often involving lungs, skin, eyes, and other organs [1-4]. Coexistence of sarcoidosis with other autoimmune or neoplastic conditions is rare [5-7]. While familial clustering of sarcoidosis is reported, the genetic and the hereditary consequences of sarcoidosis are poorly understood [8-10]. We present a case of two male sarcoidosis siblings with pulmonary, ocular, and renal involvement along with simultaneous occurrence of ulcerative colitis, and thyroid papillary carcinoma that share identical HLA-DRB1 alleles. The association of autoimmune and malignant disorders with sarcoidosis will shed light on the pathogenesis for the genetic profile of both sarcoidosis and the relevant conditions. This presentation will also provide a guide for clinicians regarding the diagnostic challenge that will arise due to the simultaneous occurrence of three irrelevant disorders. Two brothers diagnosed with simultaneous sarcoidosis, ulcerative colitis, and papillary thyroid carcinoma shared the common identical HLA-DRB1 alleles. This case report is the first in the literature to reveal the coexistence of three diseases with completely distinctive genetic and pathologic mechanisms in two siblings carrying an identical HLA-DRB1 allele. Concurrence of two extremely diverse conditions, one of autoimmune and the other of malignant origin, in two siblings with sarcoidosis will elucidate the genetic pattern and the pathogenesis involved for the simultaneous emergence of such cases.

Case I

A 38-year-old male presented with a six-month history of dry cough, dyspnea on exertion, fatigue, intermittent diarrhea, and sensitivity to light. Personal and family history did not reveal any significant disease of concern. The patient denied any significant personal and family disease history. He was a non-smoker and did not use alcohol or drugs. Physical examination revealed bilateral crackles over the lung bases, inflammation of both conjunctivae, and a two cm thyroid nodule. CBC revealed a decreased RBC of $3.92x10^3$µL and a reduced lymphocyte count of $0.7x10^3$/ µL. Laboratory tests showed a low Hct of 34%, elevated levels of creatinine 1.28 mg/dL, fibrinogen of 490 mg/dL, d-dimer of 1.67 mg/L, and a high serum ACE of 68 mg/L. Serum calcium was 9.53 mg/dL. The tuberculin test was negative although he was vaccinated with BCG. ECG displayed a regular sinus rhythm of 86/min with a normal axis. Thorax CT revealed enlarged lymph nodes in the anterior mediastinum and fibrotic linear opacities in the left upper lobe (Figure 1). Cytology of the BAL fluid demonstrated lymphocytosis with a

4.2 CD_4/CD_8 ratio. Transbronchial lung biopsy showed non-caseating granulomas compatible with sarcoidosis. Slit-lamp examination demonstrated bilateral anterior uveitis while pathologic examination of the renal biopsy sample revealed non-caseating granulomas congruent with sarcoidosis. Genetic testing detected the presence of the HLA-DRB1*01:03 allele. Serum cytokine levels of IL-4, L-6, IL-10, and TNF-α were significantly above normal. Thyroid ultrasound showed a 1.8 cm nodule while examination of the thyroid biopsy sample revealed papillary thyroid carcinoma. Colonoscopy showed diffuse colitis and pathology of the biopsy specimen confirmed the diagnosis of ulcerative colitis. The patient was commenced on systemic corticosteroids with oral 32 mg methylprednisolone for lung, kidney, and ocular sarcoidosis, with subsequent methotrexate as the maintenance treatment. Papillary thyroid carcinoma was managed surgically with total thyroidectomy, followed by radioiodine therapy. Ulcerative colitis was treated with mesalamine.

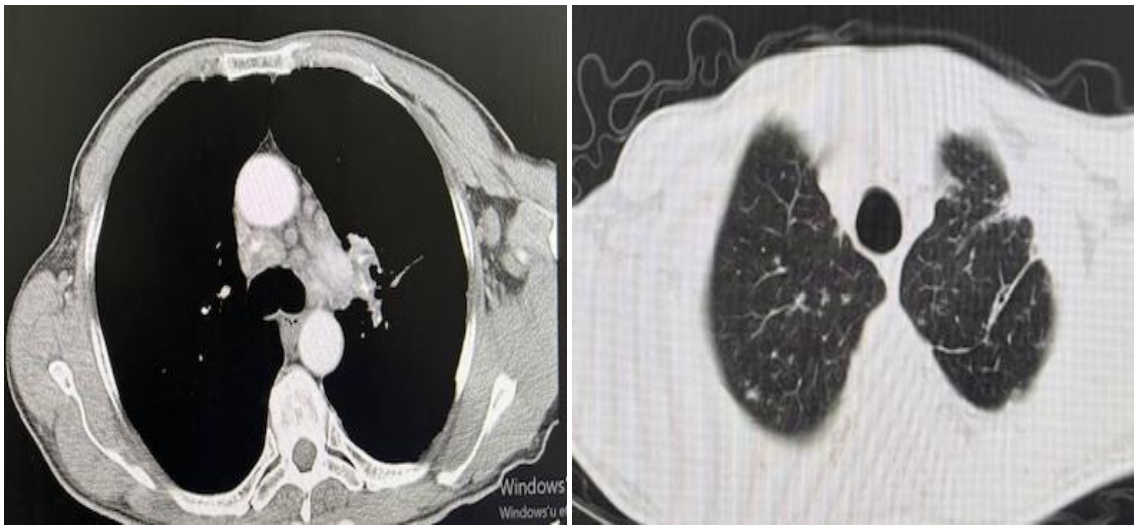

Figure 1: Thorax CT reveals multiple enlarged lymph nodes in the anterior mediastinum and parenchymal fibrotic lesions in the left upper lobe.

Case II

A 42-year-old brother presented two years later with similar symptoms including persistent dry cough, dyspnea on exertion, blurred vision, light sensitivity, and abdominal pain, Personal and family history did not reveal any significant disease. The patient was a non-smoker, and did not use alcohol or drugs. Physical examination demonstrated inflamed conjunctivae, abdominal tenderness, and a painless thyroid nodule of three cm in diameter. Laboratory studies showed a normal blood count, an elevated ERS of 21 mm/h, a CRP of 5 mg/L, and an ACE of 62 mg/L. Serum calcium was 9.58 mg/dL. The tuberculin test was negative with a 4 mm induration though the patient had a BCG vaccination. Chest x-ray revealed bilateral hilar lymphadenopathy compatible with sarcoidosis (Figure 2). Serum cytokine levels of IL-2, IL-4, IL-6, and TNF-α were markedly elevated. BAL cytology displayed lymphocytosis and a 3.8 CD_4/CD_8 ratio. Transbronchial biopsy confirmed non-caseating granulomas compatible with pulmonary sarcoidosis. Slit-lamp examination revealed bilateral anterior uveitis. The HLA typing presented the same HLA-DRB1*01:03 allele as his sibling. Colonoscopy detected segmental colitis while pathologic assessment of the biopsy sample identified ulcerative colitis. Pathologic examination of the thyroid aspiration biopsy sample demonstrated findings compatible with papillary thyroid carcinoma. The patient was given oral 32 mg methylprednisolone daily and was later transitioned to methotrexate. Papillary thyroid carcinoma was treated with total thyroidectomy with radioiodine therapy. For ulcerative colitis mesalamine and intermittent corticosteroids for flares were commenced.

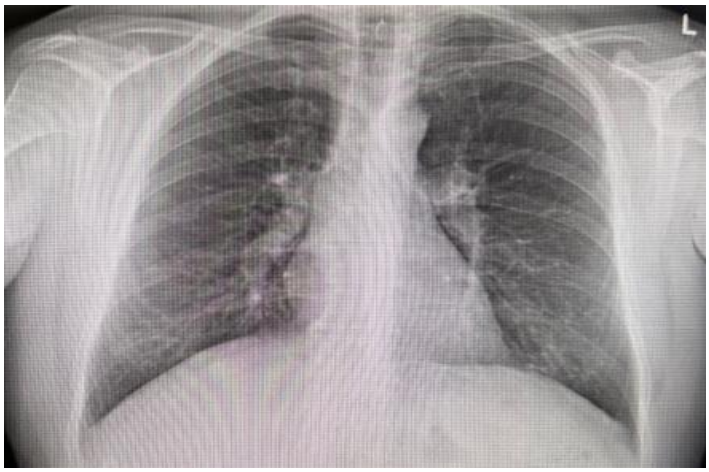

Figure 2: Chest x-ray shows bilateral hilar lymphadenopathy.

Discussion

This case highlights the coexistence of sarcoidosis, ulcerative colitis, and papillary thyroid carcinoma in two siblings with identical HLA-DRB1:03*01 alleles, suggesting a complex interplay of genetic predisposition with shared immunologic mechanisms. Each disease presents distinct yet overlapping features of immune dysregulation, implying a unifying pathogenetic pathway modulated by the common HLA-DRB1 alleles. Sarcoidosis is a granulomatous disorder with a complex etiology involving genetic, immunologic, and environmental factors [1-4]. Clustering of sarcoidosis in families and the consociate HLA-DRB1*01:03 allele in these siblings support the hypothesis of hereditary transmission. HLA-DRB1 alleles have been implicated in increased susceptibility to sarcoidosis, with variations influencing the disease presentation and progression [7-10]. Based on the same theoretical evolution of pathogenesis, the identical HLA-DRB1 alleles may have also influenced the development of ulcerative colitis and papillary thyroid carcinoma in these patients. The above alleles have been strongly linked to autoimmune and malignant conditions, including ulcerative colitis [11,12] and papillary thyroid carcinoma [13,14] previously. This allele encodes a class II major histocompatibility complex (MHC) molecule that presents specific antigens to CD4+ T cells, influencing the initiation and regulation of adaptive immune responses. Aberrant antigen presentation by HLA-DRB1*03:01 may predispose individuals to excessive T-cell activation and pro-inflammatory cytokine release, driving the immune and the pathogenetic pathway observed in such disorders that arise due to completely distinctive pathologic mechanisms.

The two extremely similar and even identical clinical profiles occurring in both siblings underline a striking familial concordance in multisystemic sarcoidosis with the associated two distinct conditions, one with an autoimmune and the other with a malignant background. The mutual HLA-DRB1*01:03 allele suggests a genetic predisposition, consistent with prior studies linking HLA-DRB1 alleles to sarcoidosis susceptibility [1-4]. Although genetic transmission of ulcerative colitis [11,12], thyroid carcinoma [13,14], and sarcoidosis via HLA-DRB1 alleles may occur [15-20] by themselves alone, sarcoidosis coexisting with ulcerative colitis and thyroid papillary carcinoma transmitted over an identical HLA-DRB1 allele has not been reported previously in the literature that makes this case unique and exclusive which raises questions about the potential shared immunopathogenic alleys. Simultaneous occurrence of three discrepant conditions with completely diverse etiologic and pathologic mechanisms under the same HLA-DRB1 allele is another hallmark of these cases. Variations in the HLA-DRB1 alleles may lead to coexistence of a significant number of significant disorders. The identical HLA-DRB1*01:03 alleles in these patients may reveal the genetic bridge for the hereditary occurrence of sarcoidosis, ulcerative colitis, and papillary thyroid carcinoma as well.

Pathogenesis of ulcerative colitis involves defects in epithelial barrier integrity, dysbiosis, exaggerated Th_1 and Th_2 responses. HLA-DRB1:03*01 allele has been linked to specific subtypes of ulcerative colitis that influence the colonic peptides presented to T-cells [21-23]. Papillary thyroid carcinoma is often associated with autoimmune thyroid diseases. Although not traditionally linked to HLA-DRB1:03*01, shared immunologic mechanisms such as chronic inflammation and dysregulated immune surveillance may contribute to carcinogenesis [24-28]. Elevated cytokine levels, particularly IFN-γ and TNF-α, in sarcoidosis and ulcerative colitis may have promoted tumorigenesis by fostering a pro-inflammatory microenvironment that may have induced a genomic instability. Multiple HLA alleles have been implicated to play a primary role for HLA-DRB1*01:03 in both Crohn's disease and ulcerative colitis. Disease location is an intrinsic aspect that is in part genetically determined as the major drive to changes in disease behavior over time. A noteworthy finding including a predominant role for class II HLA variants and heterozygous state observed in ulcerative colitis suggests an important role of the adaptive immune response in the colonic environment in the pathogenesis of ulcerative colitis [29-32]. Antigenic stimulation either by infectious or noninfectious stimuli as a causal factor may lead to ulcerative colitis along with the genetically determined HLA-DRB1 alleles.

Our case reveals the mutual pathogenetic mechanisms for sarcoidosis, ulcerative colitis, and papillary thyroid carcinoma development. Immune dysregulation leading to excessive production such as IL-12, IFN-γ, IL-17, and TNF-α may have created a pro-inflammatory milieu conducive to autoimmune processes. Increased serum levels of cytokines in both siblings justify the current clinical profile of our patients. The presence of an identical HLA-DRB1:03*01 allele in both siblings suggests a shared genetic susceptibility, influencing antigen presentation, and immune activation. This allele may act as a common genetic denominator across these immune-mediated disorders. Although there does not exist any clinical data regarding the presence of any infectious or environmental factor for the emergence of these three distinct diseases in our patients, the potential or the prospective effect or contribution of these factors on the pathogenesis cannot be disregarded. Infections, dietary antigens, or occupational exposures may also have acted synergistically with the genetic predisposition to induce disease onset in both siblings. As the clinical data of these two cases are concerned, there does not exist any other factors such as infection, dietary antigens, or occupational exposure other than the genetic transmission via HLA-DRB1 for the emergence of such a clinical profile. Shared epigenetic modifications may further influence gene expression, cytokine production, and immune cell phenotypes, contributing to disease concordance.

Conclusions

This case report underscores the hallmark genetic predisposition in sarcoidosis, particularly in familial clusters. The shared HLA-DRB1*03:01 allele in these siblings provides further evidence for the role of hereditary factors in sarcoidosis susceptibility. Further studies are needed to elucidate the genetic mechanisms of sarcoidosis and their implications. The identical HLA-DRB1*01:03 allele in these two siblings provides unequivocal evidence for the genetic transmission of sarcoidosis. The simultaneous emergence of ulcerative colitis and papillary thyroid carcinoma, one with an autoimmune and the other with

a malignant profile, with sarcoidosis under the congruent HLA-DRB1 allele sheds light on the genetic transmission along with the pathogenetic mechanisms of all three diseases emerging from extremely distinctive evolutionary portraits. The identical presence of the HLA-DRB1 allele in these two patients has an inevitable impact on the genetic transmission of sarcoidosis, ulcerative colitis, and papillary thyroid carcinoma. Although hereditary transmission appears to be the hallmark mechanism for the occurrence of these conditions, the possible contribution of infectious, occupational, or dietary antigens cannot be ignored. The two cases have clearly revealed that the common denominator or the evolutionary background of such disorders with completely distinct epigenetic developmental etiology, is the mutual existence of the HLA-DRB1:01*03 allele. Further studies are needed to elucidate the pathologic and the molecular mechanisms involved in sarcoidosis, ulcerative colitis, and papillary thyroid carcinoma along with their association with the HLA-DRB1 alleles. Genetic studies in familial sarcoidosis may elucidate the pathway leading to this complex disease and the coexisting comorbid disorders.

Author contributions

Cuneyt Tetikkurt contemplated and wrote the case report.

Halil Yanardag wrote the patient data and analyzed the test results.

Muammer Bilir prepared the imaging findings of the patients.

Umit Seza Tetikkurt evaluated the pathologic mechanisms involved in sarcoidosis, ulcerative colitis, and papillary thyroid carcinoma.

Conflicts of interest

All authors declare that they do not have any conflicts of interest associated with this case report. Authors confirm that there does not exist any supporting or funding agencies for the involved case report.

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