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The Rheumatic Manifestations in Patients with Combined Immunodeficiency

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ABSTRACT

Combined immunodeficiencies (CIDs) represent a rare group of inherited immune disorders in which defects in T- and B-lymphocyte function lead to recurrent infections, immune dysregulation, and an increased tendency toward autoimmune and rheumatologic complications.

A retrospective cross-sectional analysis was performed on 150 patients with CID, diagnosed according to the European Society for Immunodeficiencies (ESID) criteria and followed at the Children's Medical Center and Mofid Children's Hospital (Tehran, Iran) between 2009 and 2020.

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Clinical records, immunologic evaluations, and rheumatologic findings were reviewed, with particular attention to autoantibody
detection and disease frequency. Among 150 patients, 42 (28%) exhibited rheumatologic manifestations, with a higher frequency in females. Undifferentiated rheumatoid arthritis, undifferentiated juvenile idiopathic arthritis, and Kawasaki disease were the predominant conditions. Although lower lymphocyte counts and immunoglobulin levels were observed among non-rheumatologic patients, the differences were not statistically significant.

Impairments in T-cell–mediated immunity and antibody synthesis among individuals with CID hinder the recognition of autoantibody-associated rheumatologic disorders and delay diagnosis. Moreover, these conditions often present atypically in immunocompromised hosts; therefore, a vigilant clinical approach is essential for early identification and management.

Keywords: Autoimmune; Combined immunodeficiency; Inborn errors of immunity (IEI); Rheumatologic manifestations; Undifferentiated juvenile idiopathic arthritis

INTRODUCTION

Over 550 disorders are classified as inborn errors of immunity (IEI), each of which can impair the development, maturation, or function of immune cells.[1] Beyond their well-known predisposition to recurrent infections, IEIs encompass a broad spectrum of immune dysregulation, including allergic conditions, chronic inflammation, autoimmune phenomena, lymphoproliferative disorders, and malignancies.[2,3] Among these, combined immunodeficiencies (CIDs) represent a major subgroup characterized primarily by T-cell dysfunction, often accompanied by varying degrees of B-cell impairment.[4] The estimated incidence of CID is approximately 1 in 75 000- to 100 000 live births.[5] Compared with severe combined immunodeficiency (SCID), CIDs generally exhibit a milder yet heterogeneous clinical course.[6] A subset of patients with CID present syndromic features, such as ataxia-telangiectasia (AT), Wiskott–Aldrich syndrome (WAS), Nijmegen breakage syndrome, DiGeorge/velocardiofacial syndrome, Omenn syndrome, coloboma, heart defect, choanal atresia, growth or mental retardation ,genital hypoplasia, ear anomalies and or deafness (CHARGE syndrome), and Bloom syndrome.[4,7]

Collectively, CIDs with or without syndromic characteristics-account for approximately 10% to 30% of all IEIs worldwide.[8] Although infection remains the dominant clinical concern in T-cell immunodeficiencies, numerous studies have highlighted their high susceptibility to autoimmune diseases.[9] Autoimmunity and chronic inflammation are now recognized as core manifestations of IEIs, reflecting abnormal regulation of the immune response and the loss of self-tolerance mechanisms.[10,11] In IEI patients, the mechanism of autoimmunity differs depending on the molecular defects that cause immune dysregulation.[12] Clinical symptoms of autoimmunity are especially common in patients with antibody deficiencies such as selective IgA deficiency (sIgAD) and common variable immunodeficiency (CVID), though they may also occur in those with CID.[2] Several investigations have demonstrated a link between CIDs and rheumatologic disorders.[8]

Patients with T-cell–related immune deficiencies such as WAS and DiGeorge syndrome show a higher prevalence of inflammatory arthritis and juvenile idiopathic arthritis (JIA) compared with the general population. Moreover, WAS may promote autoimmune targeting of the vasculature, gastrointestinal tract, and kidneys.[2,13–15] Given these associations, this study aimed to determine the prevalence and clinical characteristics of rheumatologic manifestations among patients with CID, using data from 2 national pediatric immunology referral centers in Iran.

MATERIALS AND METHODS

Patients

This retrospective cross-sectional study included 150 patients diagnosed with CID who were referred to the Children's Medical Center Hospital and Mofid Children's Hospital (Tehran, Iran) between 2009 and 2020. Diagnosis of CID was established according to the European Society for Immunodeficiencies (ESID) .[16] Both centers serve as the main national referral hospitals for primary immunodeficiency in Iran, receiving patient

samples and clinical consultations from across the country. The study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran, and patient data were handled in compliance with institutional and national ethical standards.

Data Collection

Demographic, clinical, and laboratory data were extracted from the patients' medical records, including infection history, autoimmune and rheumatologic manifestations, and immunologic test results. A standardized questionnaire designed by the pediatric rheumatology and immunology research team was used to document rheumatologic features such as arthritis, vasculitis, rash, fever, and myalgia. Patients were categorized into 2 groups—rheumatologic and non-rheumatologic—based on established diagnostic criteria for rheumatologic diseases, which were confirmed by an expert pediatric rheumatologist. The rheumatologic group included patients presenting with at least 1 confirmed rheumatologic diagnosis.

Immunologic and Autoantibody Assays

Peripheral blood samples were obtained from all patients during clinical evaluation. Complete blood counts and differential leukocyte counts were measured using an automated hematology analyzer. Flow cytometric analysis was performed to determine lymphocyte subsets, including $CD3^+$ (total T cells), $CD4^+$ (helper T cells), $CD8^+$ (cytotoxic T cells), $CD19^+$ (B cells), and $CD16^+CD56^+$ (NK cells). Results were expressed as both absolute counts (cells/μL) and percentages of total lymphocytes. Serum immunoglobulin concentrations (IgG, IgA, IgM, and IgE) were measured by nephelometry using standard commercial kits. Autoantibody screening included antinuclear antibody (ANA), anti–double-stranded DNA (anti-dsDNA), extractable nuclear antigen antibodies (anti-ENA), anti-cyclic citrullinated peptide (anti-CCP), rheumatoid factor (RF), antineutrophil cytoplasmic antibody (ANCA), and anticardiolipin antibodies. ANA and ANCA were evaluated by indirect immunofluorescence (IIF), while the remaining autoantibodies were measured using enzyme-linked immunosorbent assay (ELISA). Cutoff values for positivity were defined according to the manufacturer's reference ranges.

Definitions

Undifferentiated rheumatoid arthritis is defined as inflammatory arthritis that does not meet the established classification criteria for rheumatoid arthritis (RA) or any other specific rheumatologic disease. Patients with undifferentiated RA typically present with 1 or more swollen joints and clinical evidence of synovitis, but their serologic and imaging findings are insufficient for definitive classification. This condition is often considered an early or transitional phase of RA, although a portion of patients may experience spontaneous remission without progressing to a defined rheumatologic disorder.[17] Undifferentiated JIA, according to the International League of Associations for Rheumatology (ILAR) classification, refers to arthritis in children younger than 16 years that persists for at least 6 weeks and either does not fulfill the criteria for any other JIA category or meets criteria for more than 1 subtype. This category represents a heterogeneous group of JIA cases in which the underlying immune dysregulation is variable but shares pathogenic mechanisms with other forms of JIA.[18]

Statistical Analysis

The SPSS software version (IBM Corporation, Chicago, IL, USA) was utilized to analyze the data. The normality of quantitative variables was assessed using the Shapiro-Wilk test. Frequencies and percentages of categorical variables were reported. Moreover, the median (P25–P75) was determined for quantitative variables. Fisher exact test was applied to investigate the association between 2 categorical variables. The Mann-Whitney *U* test was performed to evaluate the difference in a non-normal variable between 2 independent groups. A p value of less than 0.05 was considered significant.

RESULTS

Among the 150 patients diagnosed with CID, 85 (56.7%) were male. The median (P25–P75) age at the time of study participation was 8.0 (5.0–15.25) years. The median ages at disease onset, diagnosis, and diagnostic delay were 6 (2–12), 14 (6–48), and 6 (2–24) years, respectively. Of the 111 patients (74%) with consanguineous parents, 83 (76.85%) belonged to the non-rheumatologic group and 28 (66.7%) to the rheumatologic group (Table 1). A family history of immunodeficiency was present in 21 patients (14%).

As illustrated in Figure 1, the most frequent initial clinical manifestations were recurrent respiratory tract infections (48 patients), fever (23), skin lesions (16), chronic diarrhea (14), cytopenia (9), lymphadenopathy (8), candidiasis (7), and renal involvement (4). BCGosis and arthritis were each observed in 3 patients, while abscesses, failure to thrive (FTT), and meningitis occurred in 2 patients each. Eight patients presented with other uncommon manifestations as their first symptoms. Based on clinical and laboratory evaluations, the patients were divided into 2 groups: non-rheumatologic (n=108; 72%) and rheumatologic (n=42; 28%). Females were more frequent in the rheumatologic group, and this sex difference was statistically significant (p=0.033) (Table 1). The non-rheumatologic group showed a significantly younger median age at onset (5 vs 21 months; p=0.014). Although the difference in age at diagnosis did not reach statistical significance, diagnosis occurred earlier in the non-rheumatologic group (12 vs 38.5 months; p=0.001) (Table 1). Clinical manifestations of patients with CID are reported in Table 2. Moreover, Table 3 presents the spectrum of rheumatologic disorders observed among CID patients. The most common were undifferentiated RA (n=22, 52.4%), JIA (n=7, 16.7%), and Kawasaki disease (n=5, 11.9%). Several patients experienced 2 or more rheumatologic conditions concurrently. Patients without rheumatologic manifestations had higher rates of respiratory infections, sinusitis, oral candidiasis, lung and gastrointestinal involvement, splenomegaly, and FTT, whereas those with rheumatologic disorders demonstrated increased frequencies of autoimmune diseases (p<0.001), arthritis (p<0.001), central nervous system involvement (p=0.007), myalgia (p=0.006), and other systemic findings, such as skin lesions, arthralgia, otitis, lymphadenopathy, cough, and fever (Table 2).

Immunologic analyses revealed that the rheumatologic group exhibited relatively higher median counts of lymphocytes, neutrophils, $CD3^+$, $CD4^+$, and $CD8^+$ T cells, NK cells, and $CD19^+$ B cells, as well as an increased $CD4^+$:$CD8^+$ ratio and higher mean concentrations of IgG, IgA, IgM, and IgE; however, none of these differences were statistically significant (Table 4).

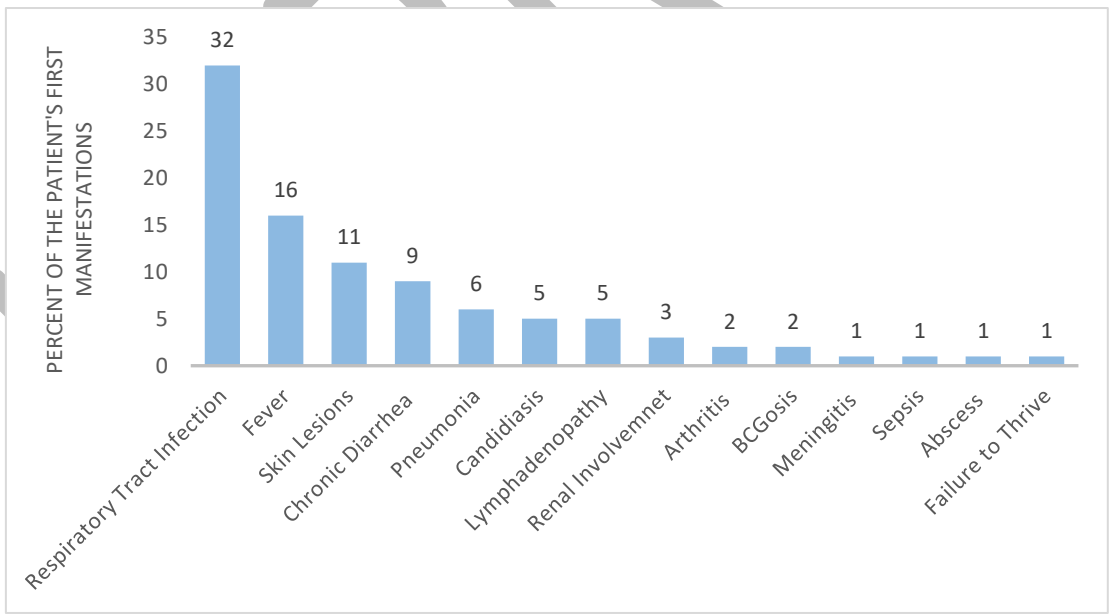

Figure 1. The first manifestation of the patients with combined immunodeficiency

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Table 1. Demographic data of patients with combined immunodeficiency

Parameters	Total (N=150)	Non-rheumatologic group (N=108)	Rheumatologic group (N=42)	*p*
Sex ratio, M/F, n	85/65 (56.6/43.3)	67/41 (62.0/38.0)	18/24 (42.9/57.1)	0.033
Family history of PID, %	142 (94.7)	101 (93.5)	41 (97.6)	0.282
Consanguinity, %	111 (74)	83 (76.85)	28 (66.7)	0.202
Dead, %	14 (9.3)	10 (9.2)	4 (9.5)	0.347
Current age, y, median (P25–P75)	8.0 (5.0–15.25)	8.0 (5.0–14.75)	8.50 (4.75–16.25)	0.538
Age at onset, y, median (P25–P75)	6 (2–12)	5 (2–8)	12 (3–24)	0.014
Age at diagnosis, y, median (P25–P75)	14 (6–48)	12 (6–28.5)	38.5 (10.5–132)	0.118
Delay in diagnosis, y, median (P25–P75)	6 (2–24)	5 (2–18)	16 (2–45.75)	0.538

F: female; M: male; PID: primary immunodeficiency disorders.

Table 2. Clinical manifestations of patients with combined immunodeficiency

Parameters	Total (N=150)	Non-rheumatologic group (N=108)	Rheumatologic group (N=42)	*p*
Pneumonia (%)	94 (62.6)	68 (62.9)	26 (61.9)	0.904
Sinusitis (%)	16 (10.6)	14 (12.9)	2 (4.7)	0.237
Malignancy (%)	1 (0.7)	0	1 (2.4)	0.280
Skin disorders (%)	58 (38.7)	40 (37)	18 (42.9)	0.511
Arthritis (%)	13 (8.7)	3 (2.8)	10 (23.8)	<0.001
Arthralgia (%)	5 (3.3)	2 (1.9)	3 (7.1)	0.134
Oral Candidiasis (%)	38 (25.3)	31 (28.7)	7 (16.7)	0.128
Alopecia (%)	5 (3.3)	4 (3.7)	1 (2.4)	1.00
Bleeding (%)	1 (0.7)	1 (0.9)	0	1.000
Myocarditis (%)	3 (2)	2 (1.9)	1 (2.4)	1.000
Vasculitis (%)	4 (2.7)	3 (2.8)	1 (2.4)	1.000
Autoimmunity (%)	19 (12.7)	7 (6.5)	12 (28.6)	<0.001
Lung Involvement (%)	107 (71.3)	78 (72.2)	29 (69)	0.699
Gastrointestinal Involvement (%)	70 (46.7)	51 (47.2)	19 (45.2)	0.827
PNS Involvement (%)	3 (2)	1 (0.9)	2 (4.8)	0.192
CNS Involvement (%)	17 (11.3)	7 (6.5)	10 (23.8)	0.007
Proteinuria (%)	4 (2.7)	2 (1.9)	2 (4.8)	0.312
Myalgia (%)	6 (4)	1 (0.9)	5 (11.9)	0.006
Otitis (%)	24 (16)	15 (13.9)	9 (21.4)	0.258
FTT (%)	61 (40.7)	49 (45.4)	12 (28.6)	0.054
Splenomegaly	41 (27.3)	31 (28.7)	10 (23.8)	0.599
Hepatomegaly (%)	38 (25.3)	29 (26.9)	9 (21.4)	0.493
Lymphadenopathy (%)	31 (20.7)	21 (19.4)	10 (23.8)	0.553
Cough (%)	51 (34)	34 (31.5)	17 (40.5)	0.269
Respiratory distress (%)	32 (21.3)	23 (21.3)	9 (21.4)	0.986
Fever (%)	61 (40.7)	42 (38.9)	19 (45.2)	0.477

CNS: central nervous system; FTT: failure to thrive; PNS: peripheral nervous system.

Table 3. The frequency of rheumatologic manifestation in patients with combined immunodeficiency

Rheumatologic disease	Total (%)	Female	Male	Parental consanguinity (N)
Familial Mediterranean fever	3 (7.1)	2	1	3
Juvenile idiopathic arthritis	7 (16.67)	5	2	4
Kawasaki	5 (11.9)	4	1	3
PFAPA	1 (2.3)	0	1	1
Juvenile dermatomyositis	2 (4.7)	1	1	1
Systemic lupus erythematosus	3 (7.1)	2	1	2
HLH	1 (2.3)	1	0	1
Mixed connective tissue disease	3 (7.1)	3	0	0
Psoriatic arthritis	1 (2.3)	1	0	0
Enthesitis-related arthritis	1 (2.3)	1	0	0
Macrophage activation syndrome	1 (2.3)	0	1	0
Undifferentiated juvenile arthritis	3 (7.1)	1	2	2
Undifferentiated rheumatoid arthritis	22 (52.38)	8	14	16

HLH: hemophagocytic lymphohistiocytosis; PFAPA: periodic fever, aphthous stomatitis, pharyngitis, adenitis.

Table 4. Immunologic profile in in patients with combined immunodeficiency

Parameters	Median (P25–P75) Total (N=150)	Non-rheumatologic group (N=108)	Rheumatologic group (N=42)	*p*
WBC (cell/µL)	7825.00 (4900.00–12992.50)	7900.00 (4777.50–13000.00)	7400.00 (5082.50–10075.00)	0.862
Absolute lymphocytes count (cells/µL)	2850.10 (1506.32–5545.00)	2814.75 (1660.93–5484.31)	3006.10 (1294.20–5918.75)	0.201
Absolute neutrophils count (cells/µL)	3183.40 (1818.00–5360.22)	3034.95 (1559.02–5536.46)	3339.86 (2302.65–5207.25)	0.629
$CD3^+$ T cells (%)	57.0 (43.0–70.4750)	50.7 (42.0–70.0)	62.0 (51.0–73.0)	0.142
$CD4^+$ T cells × 10^3 (%)	24.6 (17.2–37.0)	22.97 (17.00–36.25)	27.0 (18.0–37.0)	0.515
$CD8^+$ T cells × 10^3 (%)	23.0 (16.0–38.0)	22.8 (13.20–36.0)	25.7 (17.0–42.0)	0.336
$CD4^+/CD8^+$ ratio	1.069 (1.078–0.97)	1.005 (1.28–1.006)	1.05 (1.05–0.88)	0.153
NK cell (%)	3.50 (7.6–14.7)	7.3 (3.8–15.1)	7.60 (3.40–13.10)	0.240
$CD19^+$ B cells (%)	18.0 (6.3–29.0)	17.80 (6.0–30.9)	19.0 (8.0–25.1)	0.667
IgG (mg/dL)	592.50 (309.25–919.00)	570.00 (316.50–907.00)	711.50 (265.00–950.00)	0.575
IgA (mg/dL)	58.00 (20.75–122.25)	58.00 (20.00–117.50)	58.50 (22.00–151.75)	0.365
IgM (mg/dL)	75.00 (26.00–136.00)	72.50 (26.00–135.50)	82.00 (25.50–137.00)	0.623
IgE (IU/ml)	10.00 (2.00–65.25)	10.0 (2.00–105.00)	13.55 (2.00–45.75)	0.736

Ig: immunoglobulin; NK cell: natural killer cell; WBC: white blood cell.

DISCUSSION

This study provides the first comprehensive assessment of rheumatologic manifestations among Iranian patients with combined immunodeficiency. The rheumatologic involvement was observed in 28% of our cohort with undifferentiated JIA, representing the most frequent manifestation.

The coexistence of autoimmune or rheumatologic disorders in patients with IEI is increasingly recognized, highlighting the overlapping molecular pathways that regulate immune tolerance and inflammatory responses. Genetic and immunologic studies have revealed shared mechanisms between primary immunodeficiencies (PIDs) and autoimmune diseases, such as RA, where alterations in immune-regulatory genes contribute to

both impaired pathogen defense and loss of self-tolerance.[19] Our findings closely align with those reported by Fischer et al, who analyzed 2183 patients with primary immunodeficiency and demonstrated that approximately 26.2% had at least 1 autoimmune or inflammatory manifestation, with combined immunodeficiencies showing one of the highest rates among all PID categories.[20] In our cohort, 28% of patients exhibited rheumatologic or autoimmune features, a proportion that is remarkably similar to Fischer's observations. This concordance reinforces the notion that immune dysregulation and rheumatologic involvement are intrinsic features of combined immunodeficiency and not limited to specific populations or geographic regions. Both studies collectively highlight that impaired immune tolerance and abnormal activation of lymphocytes contribute substantially to the autoimmune spectrum in CID patients.

The prevalence of rheumatologic disorders among patients with PID has been estimated at 5000 per 100 000, compared with 860 per 100 000 in the general population, corresponding to a relative risk of 6.[20] Furthermore, the relative risk of RA was reported to be 40 times higher in patients with PID compared with healthy controls. Rheumatologic disorders in CID patients appear paradoxical, as immune deficiency theoretically reduces autoreactive lymphocyte activity; however, defective immune regulation may instead promote persistent inflammation and autoimmunity. This imbalance between immune activation and suppression can result in atypical or refractory rheumatologic disease courses.[14] There are usually more aggressive forms of rheumatologic disease associated with a PID. Based on recent evaluations of rheumatology clinics, 14% to 22% of their patients had PID.[13] The present study aligns with previous observations showing that autoimmunity and inflammation are key noninfectious complications of primary immunodeficiencies. None of our patients presented with rheumatologic symptoms as their initial feature; rather, recurrent respiratory infections, fever, skin lesions, and chronic diarrhea were the most common presenting symptoms. This pattern mirrors findings from previous Iranian cohorts, in which pulmonary and gastrointestinal infections predominated, followed by autoimmune manifestations and splenomegaly as the most frequent noninfectious complications.[21,22] Although CID is typically more prevalent in males, our results showed a female predominance among patients with rheumatologic disorders, consistent with prior reports.[21] This female predominance in rheumatologic manifestations likely reflects the combined effects of sex hormones (notably estrogen), X-linked immune genes, and sex-specific epigenetic regulation—mechanisms that have been well described in recent high-quality reviews.[23,24]

The most frequent rheumatologic diseases identified were undifferentiated RA, undifferentiated JIA, and Kawasaki disease. The high prevalence of undifferentiated arthritis may stem from diagnostic challenges due to atypical serologic profiles in immunodeficient individuals, in whom autoantibodies may be absent or below detectable thresholds. This finding underscores the importance of relying on clinical rather than serological criteria when evaluating autoimmune diseases in patients with CID.

Autoimmunity in CID can manifest in various organ systems. For instance, autoimmune neutropenia occurs in nearly half of patients with hyper-IgM syndrome. Those with activated phosphoinositide 3-kinase δ syndrome (APDS) often exhibit autoimmune cytopenias, arthritis, and gastrointestinal inflammation, while inducible costimulatory (ICOS) deficiency has been associated with arthritis and cytopenias in up to 75% of cases.[15] Such overlap highlights the role of aberrant lymphocyte signaling and impaired apoptosis in the pathogenesis of autoimmunity within CID. Case reports and cohort studies have also described autoimmune and autoinflammatory manifestations such as arthritis, pericarditis, and vasculitis in patients with CID-related disorders, including APDS and WAS.[21,25] Collectively, these data support our observation that immune dysregulation, rather than infection alone, contributes significantly to disease burden in this population.

Figure 1 shows the first manifestation of the patients with combined immunodeficiency.

This study has several limitations. First, genetic confirmation was unavailable for a portion of patients, as most diagnoses were based on ESID/PAGID clinical and immunologic criteria. Consequently, we were unable to perform genotype–phenotype correlation analyses. Second, some patients were lost to follow-up, potentially introducing survival bias. Finally, therapeutic interventions such as immunoglobulin replacement or corticosteroid therapy could have influenced immunologic results. Despite these

limitations, the inclusion of patients from 2 expert national centers enhances the representativeness of our sample and supports the generalizability of our findings to the broader Iranian CID population.

In summary, patients with CID exhibit a considerable prevalence of rheumatologic manifestations, most commonly undifferentiated arthritis and Kawasaki disease. Impaired T-cell function and antibody production complicate the identification of autoantibodies and delay diagnosis. Moreover, rheumatologic presentations in immunocompromised individuals are often atypical and diagnostically challenging. Therefore, clinicians should maintain a high index of suspicion and consider underlying immunodeficiency when assessing rheumatologic disorders, especially in patients with recurrent or atypical presentations.

STATEMENT OF ETHICS

Shahid Beheshti University of Medical Sciences Ethics Committee approved the study.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

Derived data supporting the findings of this study are available from the corresponding authors [RSH or SSH] on request.

AI ASSISTANCE DISCLOSURE

We acknowledge the use of ChatGPT for sentence improvement and language editing. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

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