Distinct features of trisomy 8-associated autoinflammatory disease from Behçet's disease: case series and systematic review

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Abstract

Objective

To characterise patients with trisomy 8 presenting with autoinflammatory features, comparing them to patients with Behçet's disease (BD).

Methods

We comprehensively reviewed studies on trisomy 8-associated autoinflammatory symptoms from four online databases and analysed clinical data from both published cases and our institution. We then compared the clinical features of these patients with those of 657 BD patients from the Yokohama City University Registry.

Results

Of 1,542 screened articles, 88 involving 181 patients were eligible, along with six additional patients from our institution, resulting in a total of 187 patients included. Fever was the most common symptom in patients with trisomy 8 (85.8%), followed by oral ulcers (80.8%), gastrointestinal lesions (76.1%), genital ulcers (54.7%), and skin lesions (53.7%). Compared to BD patients, trisomy 8 patients exhibited higher rates of fever and gastrointestinal involvement ($p<0.001$), but lower rates of oral and genital ulcers, uveitis, and skin involvement ($p<0.001$), with no significant difference in joint symptoms. Trisomy 8 patients were older and had lower haemoglobin levels, increased mean corpuscular volume, decreased platelet counts, and higher C-reactive protein levels than BD patients. Additionally, the mortality rate was significantly higher in trisomy 8-positive patients (odds ratio, 11.74; 95% confidence interval, 5.94–22.82).

Conclusion

Trisomy 8-associated autoinflammatory disease patients were older and had poorer prognoses, more gastrointestinal involvement, and less frequent oral and genital ulcers and skin involvement, making BD diagnosis less likely. Bone marrow examination should be considered for late-onset BD-like disease patients, particularly with recurrent fever.

Key words

trisomy 8, Behçet's syndrome, myelodysplastic syndromes, clonal haematopoiesis

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Introduction

Behçet's disease (BD) is an idiopathic autoinflammatory disorder characterised by oral ulcers, genital ulcers, erythema nodosum-like skin rash, folliculitis-like skin rash, and uveitis. In some cases, gastrointestinal, neurological, and vascular lesions accompany the disease, making organ damage problematic. The disease is considered heterogeneous, with a mixture of patients suffering from different aetiologies (1). Myelodysplastic syndromes (MDS) are diseases characterised by abnormal clonal haematopoiesis and dysplasia due to genetic mutations in haematopoietic stem cells, resulting in one or more cytopenias. Trisomy 8 is one of the most frequent genetic mutations observed in MDS (2). For decades, it has been reported that MDS patients with trisomy 8 can develop intestinal BD. In recent years, however, cases have been reported where patients develop intestinal BD even without the cytopenias typical of MDS but with trisomy 8 mutations in their hematopoietic stem cells - a condition known as clonal cytopenia of undetermined significance (CCUS) or clonal haematopoiesis of indeterminate potential (CHIP) (3, 4). In addition, several trisomy 8-positive cases have been reported to have a phenotype different from BD, such as periodic fever (5-7), pulmonary alveolar proteinosis (8-10), and interstitial pneumonia (11-13). These findings suggest that there are potentially many patients with autoinflammation related to trisomy 8. Therefore, we performed a systematic literature review to investigate the clinical features of trisomy 8-associated autoinflammatory disease in patients with and without a diagnosis of BD or MDS. Additionally, we compared the characteristics of trisomy 8-associated autoinflammatory pathology with those of patients in our BD registry.

Methods

Patients of the Yokohama City University institutional database

Consecutive trisomy 8 patients with autoinflammatory conditions at the rheumatology department of Yokohama City University Hospital between May 2007 and October 2023 were included. The study was approved by the ethics committee of Yokohama City University (A121129002, F220300051). We have acquired the clinical data from the patient's medical records and the electronic database. The study followed the Ethical Guidelines for Epidemiology Research, published by the Japanese Ministry of Health, Labour and Welfare (14). Informed consent was obtained through an opt-out process in accordance with institutional ethical guidelines. Additionally, written consent was obtained from five participants who actively agreed to partake in the study. To compare clinical features between trisomy 8 patients and BD patients, we used a previously described BD registry from the Yokohama City University Hospital (15).

Systematic literature review

We performed a systematic review of the literature using PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and the Web of Science Core Collection (up to December 14th, 2023) for autoinflammatory symptoms in adult patients with trisomy 8. The search formulas are presented in the Supplementary Text. KI and SA independently screened the candidate articles by reviewing the title and abstract after uploading the citation list to Endnote X9 software (Thomson Reuters, Philadelphia, PA, USA) and Rayyan (https://www.rayyan.ai/). Any discrepancy between the two reviewers was first resolved by discussion, and a third reviewer (KT-M) adjudicated it when no consensus was reached. The inclusion criteria were as follows: (1) adult patients clinically diagnosed with autoinflammatory conditions associated with trisomy 8; (2) published Case reports, case series, case-control studies, and cohort studies; and (3) describing fever, oral ulcers, genital ulcers, skin lesions, arthralgias, and intestinal lesions. Studies published in languages other than English were excluded. This systematic review was registered in the University Hospital Medical Information Network Center Clinical Trial Registry (Japan) (UMIN000053104) (16).

Data extraction and statistical analyses

The following data were extracted: patients' age and gender, the timing of diagnosis of trisomy 8, symptoms, involved organs, cytogenetics, C-reactive protein (CRP) and complete blood count at diagnosis, HLA-B51 status, complications of MDS, treatment, response to treatment, and outcome. The procedures for data extraction were conducted by an independent pair of reviewers (KI and SA) and verified by a third reviewer (KT-M).

We compared demographics, clinical symptoms, treatment data, and outcomes between trisomy eight patients and BD patients. Categorical variables were analysed using Fisher's exact test. Continuous variables were examined using the Mann-Whitney U-test. The log-rank test was used to compare the survival time from symptom onset. A *p*-value less than 0.05 was considered statistically significant. Finally, odds ratios (ORs) with 95% confidence intervals (CIs) were determined for each variable. Statistical analysis was performed using GraphPad Prism (v. 9.5.1; GraphPad Software, La Jolla, CA, USA).

Results

Case presentation

Our institutional cohort identified six cases of trisomy 8 with autoinflammatory symptoms. All six patients were Asian Japanese, and one was female, with a mean age of 73.3±7.39 years. MDS was a complication in three of six cases. Three patients had recurrent periodic fevers; one was diagnosed with intestinal BD; one had multiple intraoral ulcers, an impetigo-like skin rash, and periodic fevers, which were complicated by multiple ulcers in the ileum and ascending colon (Fig. 1). This case is a 75-year-old man with persistent oral ulcers, skin rashes, and recurrent fevers was transferred to our hospital with suspected incomplete BD. Glucocorticoid treatment improved his skin symptoms, and additional immunosuppressants were administered. However, severe bleeding from intestinal ulcers persisted, and he passed away 32 days after the transfer. One was diagnosed with Sjögren's syndrome. All were treated with glucocorticoids; colchicine was used in two cases for skin and mucous membrane symptoms; methotrexate was used in one case for arthritis; and 5-aminosalicylic acid and infliximab were introduced in two cases with intestinal lesions. Glucocorticoid treatment resistance was seen in five cases, candidiasis was complicated in one case, and an intra-abdominal abscess occurred in one case. Despite multidisciplinary treatment, one patient died due to gastrointestinal bleeding

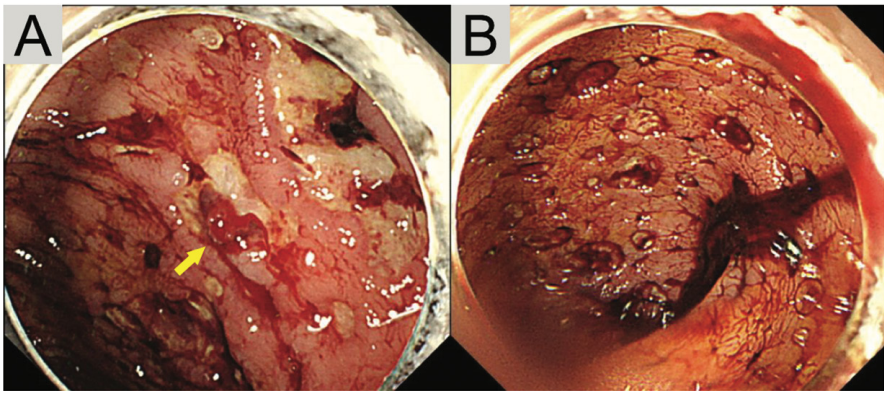

Fig. 1. Colonoscopy of trisomy 8-associated autoinflammatory disease with intestinal Behçet's disease-like lesions at our institution.
A: Multiple ulcers are observed in the ileocecal region. Deep punched-out ulcers with loss of mucosal layer are present, with partial exposure of the fat layer. An exposed blood vessel is visible in the centre of the image (arrow).
B. Deep punched-out ulcers are found not only in the ileocecal region but also in the ascending colon.

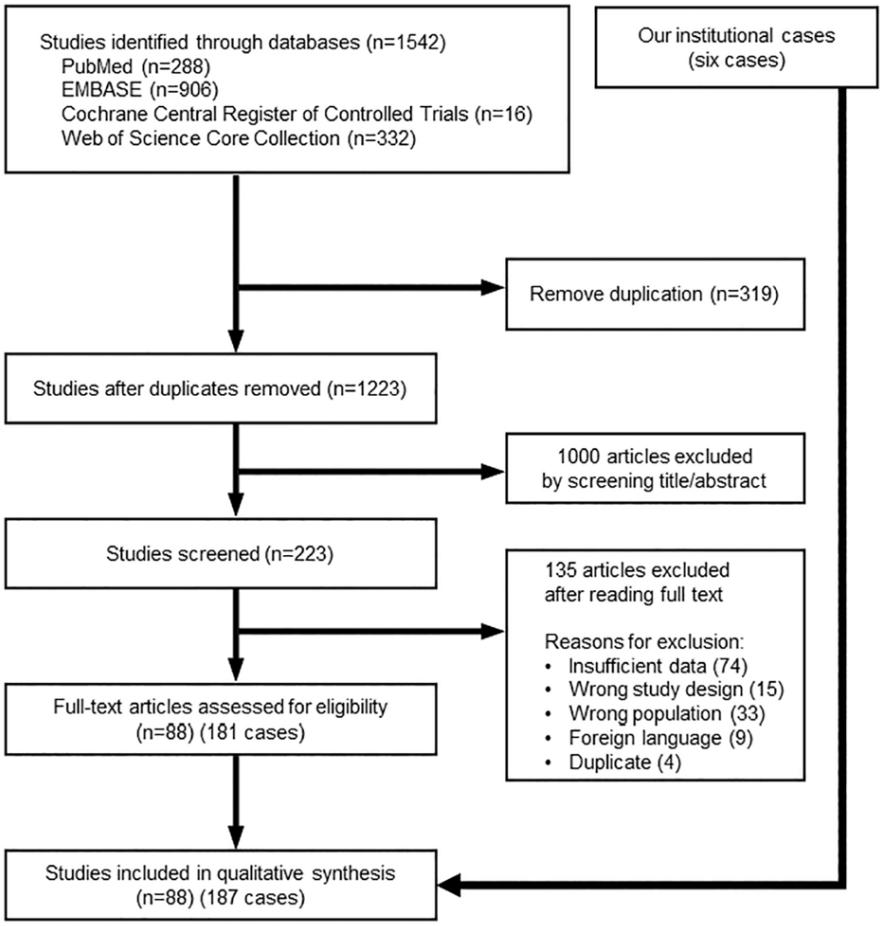

Fig. 2. Study selection flow chart.

Table I. Clinical features of trisomy 8-associated autoinflammatory disease (Trisomy 8) and Behçet's disease (BD).

Variables	Trisomy 8 (n=187)	BD (n=657)	*p*-value	Odds ratio (95% CI)
East Asia, n (%)	128 (68.4)			
	Japan: 71, China: 46, Korea: 10, Taiwan: 1	657 (100)	<0.0001	0.00 (0.00-0.012)
Age at onset, mean ± SD	52.9 ± 17.7	36.6 ± 12.3	<0.0001	-
Observation period (year), mean ± SD	2.1 ± 3.1	13.7 ± 11.8	<0.0001	-
Female, n (%)	100 (53.5)	372 (56.6)	0.45	0.88 (0.63-1.22)
Clinical phenotypes				
Fever, n (%)	103/120 (85.8)	N/A	-	-
Oral ulcer, n (%)	122/151 (80.8)	653 (99.4)	<0.001	0.026 (0.010-0.073)
Genital ulcer, n (%)	76/139 (54.7)	474 (72.1)	<0.001	0.47 (0.32-0.68)
Eye involvement, n (%)	8/112 (7.1)	392 (59.7)	<0.001	0.052 (0.025-0.104)
Skin involvement, n (%)	80/149 (53.7)	585 (89.0)	<0.001	0.14 (0.095-0.214)
Erythema nodosum, n (%)	27/149 (18.1)	N/A	-	-
Pseudofolliculitis, n (%)	13/149 (8.7)	N/A	-	-
Other skin symptom, n (%)	23/149 (15.4)	N/A	-	-
Joint involvement, n (%)	59/119 (49.6)	301 (52.1)	0.48	1.16 (0.79-1.70)
Gastrointestinal involvement, n (%)	121/159 (76.1)	113 (17.2)	<0.001	15.33 (10.02-23.14)
Neurological involvement, n (%)	2/47 (4.3)	67 (10.2)	0.37	0.39 (0.088-1.43)
Vascular involvement, n (%)	Vasculitis: 5/51 (9.8)	55 (8.4)	-	-
Other organ involvement, n (%)	Lung involvement: 12/21 (57.1)	Epididymitis: 15/285 (5.3)	-	-
Laboratory data, mean ± SD				
White blood cells (10^9/L)	8.57 ± 9.06	6.93 ± 2.40	0.029	-
Haemoglobin (g/dL)	10.1 ± 9.7	13.2 ± 1.6	<0.0001	-
Mean corpuscular volume (fL)	106.3 ± 13.0	89.1 ± 5.5	<0.0001	-
Platelets (10^9/L)	149 ±180	546 ± 839	<0.0001	-
C-reactive protein (mg/dL)	12.1 ± 9.9	0.69 ± 1.50	<0.0001	-
Other characteristics				
HLA-B51 positivity, n (%)	12/38 (31.6)	214/449 (47.7)	0.063	0.51 (0.26-1.04)
MDS, n (%)	161/179 (89.9)	N/A	-	-
Fulfilling ISG criteria, n (%)	38/69 (55.1)	583 (88.7)	<0.0001	0.16 (0.093-0.26)
Fulfilling ITR-ICBD criteria, n (%)	60/77 (77.9)	645 (98.2)	<0.0001	0.067 (0.030-0.15)
Treatments				
Colchicine, n (%)	15/172 (8.7)	375/522 (71.8)	<0.0001	0.040 (0.022-0.065)
Corticosteroid, n (%)	120/172 (69.8)	236/522 (45.2)	<0.0001	2.80 (1.93-4.10)
Salazosulfapyridine, n (%)	11/172 (6.4)	N/A	-	-
5-aminosalicylic acid, n (%)	19/172 (11.0)	N/A	-	-
Immunosuppressants, n (%)	44/172 (25.6)	203/522 (38.9)	0.0013	0.54 (0.36-0.79)
Biological agents, n (%)	20/172 (11.6)	95 (14.5)	<0.0001	0.18 (0.076-0.43)
Janus kinase inhibitors, n (%)	5/172 (2.9)	N/A	-	-
Chemotherapy, n (%)	63/172 (36.6)	N/A	-	-
Azacitidine, n (%)	31/172 (18.6)	N/A	-	-
Allogeneic hematopoietic stem cell transplantation, n (%)	24/172 (14.0)	N/A	-	-
Bone marrow transplantation, n (%)	8/172 (4.7)	N/A	-	-
Peripheral blood stem cell transplantation, n (%)	7/172 (4.1)	N/A	-	-
Cord blood transplantation, n (%)	5/172 (2.9)	N/A	-	-
Outcomes				
Death, n (%)	20/64 (31.3)	22/590 (3.7)	<0.0001	11.74 (5.94 to 22.82)
Infection, n (%)	15/64 (23.4)	5/590 (0.85)	<0.0001	35.82 (13.30-91.52)
Haemorrhage, n (%)	5/64 (7.8)	2/590 (0.34)	<0.0001	24.92 (5.14-126.0)
Disease progression and transformation to AML, n (%)	5/64 (7.8)	0/590 (0.0)	<0.0001	infinity (14.31-infinity)
Other reasons, n (%)	0/64 (0.0)	15/590 (2.5)	0.38	0.00 (0.00-2.23)

MDS: myelodysplastic syndromes; ISG: International Study Group; ITR-ICBD: International Team for the Revision of the International Criteria for Behçet's Disease; AML: acute myeloid leukaemia.

and another due to the progression from MDS to acute leukaemia. The clinical symptoms, treatments, and outcomes of the six cases are detailed in Supplementary Tables S1 and S2.

Overview of systematic review and analysed cases

Of the 1,542 candidate articles, 88 manuscripts met the inclusion criteria, reporting 181 trisomy 8 cases (Fig. 2). Additionally, six cases from our institutional cohort were included. Thus, a total of 187 cases were analysed. The characteristics of the included studies are summarised in Table I. Their mean

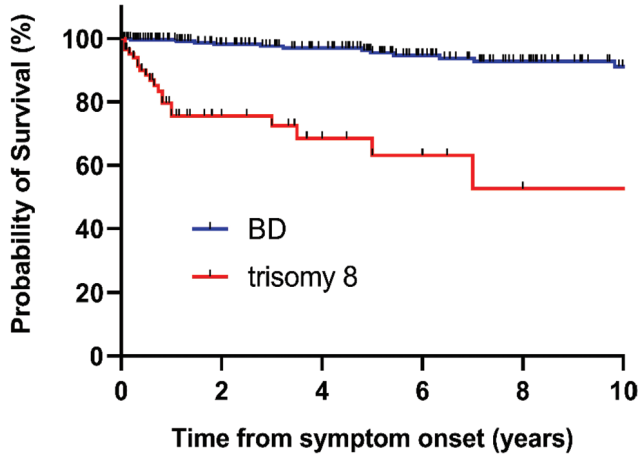

Fig. 3. Kaplan-Meier plot showing survival from symptom onset.
Kaplan-Meier survival curves estimating overall survival probabilities for patients with trisomy 8-associated autoinflammatory disease compared to those with BD. The 10-year survival rates were 52.6% for trisomy 8-associated autoinflammatory disease and 91.2% for BD. The log-rank test yielded a hazard ratio (HR) of 7.3 (95% confidence interval 3.0-18.2, $p<0.0001$).

age ± SD at the time of diagnosis of trisomy 8 was 52.9±17.7. In patients with trisomy 8, fever was the most common finding (85.8%), followed by oral ulcers (80.8%), gastrointestinal lesions (76.1%), genital ulcers (54.7%), skin lesions (53.7%), arthralgia (49.6%), and uveitis (7.1%). The complication rate of MDS was 89.9% (Suppl. Fig. S3).

Comparison of trisomy 8 and BD clinical features

We used data from BD registry accumulated at our institute to compare the clinical features of trisomy 8 and BD. Patients with trisomy 8 were significantly more likely to have a fever and gastrointestinal involvement than BD patients ($p<0.001$). Oral and genital ulcers, uveitis, and skin involvement were less frequent in trisomy 8 patients than in BD patients ($p<0.001$), and there were no significant differences in joint symptoms. In the univariate analyses, patients with trisomy 8 were older than patients with BD ($p<0.001$). Blood tests showed that patients with trisomy 8 had lower haemoglobin levels, increased mean corpuscular volume (MCV), decreased platelet counts, and increased CRP levels compared to patients with BD ($p=0.0052$ for haemoglobin levels, $p<0.001$ for platelet counts, $p<0.001$ for MCV, and $p<0.001$ for CRP). White blood cell (WBC) counts showed a statistically significant difference between the two groups ($p<0.029$). However, while the mean WBC count was higher in the trisomy 8 group, the median value was lower compared to the BD group (trisomy 8 (n=73): mean ± SD: 8.57±9.06 × 10^9/L, median: 5.17 × 10^9/L; BD (n=420): mean ± SD: 6.93±2.40 × 10^9/L, median: 6.60 × 10^9/L). Further analysis of the WBC count distribution revealed a bimodal pattern in the trisomy 8 group (Suppl. Fig. S1). Trisomy 8 patients showed less fulfilling International Study Group for Behçet Disease (ISG) criteria (16) and International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD) criteria (18).

Treatment

Treatment details were available for 173 cases of trisomy 8 and 522 cases of BD (Supplementary Table S2). Compared to BD, trisomy 8 had a lower rate of colchicine use (9.2% *vs*. 71.8%) and a higher rate of corticosteroid use (69.4% *vs*. 45.2%). For the treatment of trisomy 8, some cases used corticosteroid, colchicine, 5-aminosalicylic acid, salazosulfapyridine, azathioprine, and tumour necrosis factor inhibitors (TNFi), similar to the treatment for intestinal BD. Other medications used included cyclophosphamide, tacrolimus, cyclosporine A, methotrexate, and iguratimod. Among biological agents, there was one case of ustekinumab use, while all others were TNFi. Cases using Janus kinase inhibitors were also observed, with all cases showing improvement (tofacitinib: 2, baricitinib: 1, ruxolitinib: 1, data not shown). As for chemotherapy, azacitidine was used in 17.9% of cases.

Outcomes

Outcome data were available for 64 cases in the trisomy 8 group and 590 in the BD group (Suppl. Table S2). The mortality rate was significantly higher in trisomy 8-positive patients compared to those with BD (OR 11.74; 95% CI 5.94–22.82). Although bias elimination was not possible due to the inclusion of only case reports, survival time analysis was performed. The 10-year survival rate was 52.6% for trisomy 8 *vs*. 91.2% for BD, with the Log-rank test showing HR 7.3 (95% CI 3.0-18.2, $p<0.0001$) (Fig. 3).

Discussion

Although several systematic reviews on trisomy 8 have been conducted, this study is the first to elucidate the distinctions in autoinflammatory pathology between trisomy 8 mosaicism and BD, including uncomplicated cases of MDS.

Trisomy 8-associated autoinflammatory disease primarily affects older adults, in contrast to BD, which typically occurs in younger individuals (1). This age disparity may be attributed to the accumulation of genetic mutations in hematopoietic stem cells over time. Clinical features like advanced age, fever, macrocytic anaemia, and thrombocytopenia are more common in trisomy 8-associated autoinflammatory disease than in BD. The bimodal distribution of WBC counts in the trisomy 8 group likely reflects two distinct subpopulations: one with cytopenia due to dysplasia caused by the abnormal clone, and another with leukocytosis attributed to inflammation or progression to acute myeloid leukaemia (AML). These differences imply that trisomy 8-associated disease has distinct aetiology, treatment, and prognosis from BD and should be investigated as a separate disease entity.

Trisomy 8-associated autoinflammatory disease affects many of the same or-

gans as BD, including the skin, joints, eyes, blood vessels, nervous system, and intestines, with the addition of pulmonary involvement. However, its dermatological features are distinct from BD, presenting with non-specific inflammatory lesions (9, 13, 19). Multiple cases of anti-GM-CSF antibody-negative pulmonary alveolar proteinosis were reported (8-10), a feature shared with GATA2 deficiency syndrome, which also presents with MDS and inflammatory conditions (20). Several cases demonstrated trisomy 8-positive cell infiltration in caecal mucosa (21), bronchoalveolar lavage fluid (22) and mucocutaneous ulcers (23) via fluorescence in situ hybridisation (FISH) analysis. It has been reported that upregulation of proinflammatory genes in trisomy 8-positive MDS patients suggests these clones (24), may directly cause organ damage or disrupt systemic inflammation control. Previous studies have demonstrated a strong association between MDS and inflammation, with elevated levels of inflammatory cytokines (25). Clonal haematopoiesis of indeterminate potential (CHIP) also correlates with an increased risk of cardiovascular events (26), suggesting aberrant clones contribute to inflammation. In MDS, activation of the nuclear factor kappa B (NF-κB) signalling pathway has been observed (27, 28). In A20 haploinsufficiency, reduced A20 levels lead to heightened NF-κB activity and BD-like symptoms (29). Thus, enhanced NF-κB signalling in abnormal bone marrow clones, including trisomy 8, is a key pathogenic mechanism and a potential therapeutic target. While inflammatory conditions have been reported in MDS patients with various karyotypes, trisomy 8 mosaicism is notably associated with BD-like intestinal lesions, particularly in the ileocecum (30, 31). This observation suggests the presence of a promoting factor on chromosome 8, though the exact mechanism is unclear. The pathogenesis of trisomy 8-associated inflammation may involve complex mechanisms beyond mere overexpression of chromosome 8 genes, potentially encompassing epigenetic alterations. MDS often features splicing machinery mutations, such as *ZRSR2*, crucial for zinc regulation (32). Zinc dysregulation may lead to splicing abnormalities and impaired inflammation control, similar to *GATA2* deficiency (33). This is supported by a case where zinc supplementation improved symptoms in a trisomy 8-positive patient with a *ZRSR2* mutation (4). The number of trisomy 8-positive patients included in our systematic review was limited regarding cases with detailed gene mutation data. Only one case of a *ZRSR2* mutation was identified, no cases of *GATA2* deficiency were observed, and no specific trends were noted for other genetic mutations (Supplementary Figure S2). Improvements in inflammatory conditions following MDS treatment were reported in some cases (34-41). Azacitidine reported efficacy in both cytopenia and inflammatory manifestations, though the anti-inflammatory mechanism remains unclear. Haematopoietic stem cell transplantation improved haematopoiesis and inflammation, supporting the concept of genetic mutations in hematopoietic stem cells as the underlying cause. Infection was the predominant cause of death in our study, likely due to immunodeficiency associated with the abnormal clone. Despite the use of biological agents and JAK inhibitors, cases of fatal bleeding were included in this study, suggesting that gastrointestinal lesions in trisomy 8-associated autoinflammatory disease may be more refractory to treatment compared to intestinal BD. However, potential publication bias should be taken into consideration when interpreting these findings.

This study primarily included reports from Asian populations, which may be influenced by selection bias. Trisomy 8-associated autoinflammatory disease may occur across all ethnicities and could potentially be misdiagnosed as other inflammatory conditions, including Crohn's disease, ulcerative colitis, familial Mediterranean fever, seronegative rheumatoid arthritis, polyarteritis nodosa, or Sweet's syndrome. The reported increase in intestinal BD in Japan may reflect an increase in trisomy 8-associated inflammatory disease due to an aging population with accumulating haematopoietic stem cell mutations (15). The requirement for bone marrow examination to detect trisomy 8-positive abnormal clones presents a significant diagnostic challenge. This invasive procedure constitutes a barrier to efficient diagnosis and may delay appropriate intervention in affected patients. Given these challenges, it is crucial to consider bone marrow examination in patients presenting with atypical BD accompanied by advanced age, fever, macrocytic anaemia, and thrombocytopenia, as well as in those with unexplained fever and skin rashes, even in the absence of cytopenia or dysplasia.

Limitations of this study include publication bias, reliance on case reports and series, and the inability to perform meta-analysis due to study heterogeneity. Additionally, our BD registry may include patients with trisomy 8, as bone marrow examinations were not performed on all patients, potentially affecting comparative analysis. Thus, statistical comparisons between the trisomy 8 and BD groups should be interpreted cautiously due to cohort differences and possible overlap. The concept of trisomy 8-associated autoinflammatory disease remains unclear, emphasising the need for international standardisation of its definition and diagnostic criteria.

In conclusion, this study highlights potential differences in phenotype, treatment response, and prognosis between trisomy 8-associated autoinflammatory disease and BD. Establishing and standardising this disease concept internationally is crucial. The findings underscore the importance of considering bone marrow examination in patients with atypical presentations, particularly those with features suggestive of trisomy 8-associated autoinflammatory disease.

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