Case report

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Is the combination of Myelodysplastic syndromes and pulmonary fibrosis accidental or inevitable?

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ABSTRACT

Introduction: We diagnosed and managed a patient with pulmonary fibrosis combined with myelodysplastic syndrome (MDS). This paper aims to investigate, through analysis of our clinical case, a review of the existing literature, and relevant genetic analyses, whether the concurrent occurrence of pulmonary fibrosis and MDS represents a clinical coincidence or reflects an underlying shared pathogenetic mechanism.

Case Presentation: A 64-year-old male farmer with concurrent MDS and interstitial pulmonary fibrosis underwent whole-exome sequencing, which revealed abnormalities in the MTHFR, PCSK9, and IFIH1 genes. A literature review demonstrated that these three genes are associated with both MDS and pulmonary fibrosis. A search of previous literature identified six similar case reports over a 22-year period, suggesting that the concurrent occurrence of these two conditions may be linked to CD68+ cells, myeloperoxidase (MPO)-positive inflammatory cells, VEXAS syndrome, telomere diseases, and other factors.

Conclusion: MTHFR, IFIH1, PCSK9 and CTC1 are involved in key pathways including folate metabolism, immune regulation, inflammatory responses and telomere disorders, which may contribute to the pathogenesis of both MDS and pulmonary fibrosis. The coexistence of these two conditions is likely attributed to complex interactions among multiple gene mutations, environmental triggers, and dysregulated immune processes, rather than a single.

Key words: Myelodysplastic syndromes, pulmonary fibrosis, MTHFR, PCSK9, IFIH1

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Pulmonary fibrosis is a pulmonary disease that has attracted increasing attention in recent years due to its unknown etiology and high mortality rate. Myelodysplastic syndromes (MDS) are a common type of hematological disorder. Is there an association between these two diseases? Since the first report of the concurrent occurrence of the two diseases in 2003[1], relevant case reports have continued to emerge. This article presents a review of a patient admitted to our hospital six months ago. Using "pulmonary fibrosis" and "myelodysplastic

syndromes" as key terms, a literature search was conducted on PubMed, yielding six analogous clinical case reports. This paper aims to investigate, through analysis of our clinical case, a review of existing literature, and relevant genetic analyses, whether the concurrent occurrence of pulmonary fibrosis and MDS represents a clinical coincidence or reflects an underlying shared pathogenetic mechanism.

Case presentation

A 64-year-old male farmer was admitted to the hospital on January 13, 2025, due to intermittent cough and dyspnea for 1 month, accompanied by fever for 1 week. One month prior to admission, the patient developed an intermittent cough without obvious predisposing factors, accompanied by general weakness and mild dyspnea. The cough was non-productive, without sputum or hemoptysis, and previous oral amoxicillin treatment yielded no improvement. One week before admission, the patient developed fever and expectoration, with a maximum body temperature of 39°C, along with aggravated cough and dyspnea. The patient denied any previous surgical history or allergies. There was no significant family history. Physical examination revealed a temperature of 38.6°C, coarse breath sounds in both lungs, and audible crackles. Laboratory examinations: the routine blood test showed anemia and a significant decrease in platelets (Table 1, 2025-01-14); Procalcitonin: 0.276 ng/ml, C-reactive protein 151.49 mg/L, IL-6 197 pg/ml; Liver and kidney function, myocardial enzymes, electrolytes, and coagulation parameters showed no obvious abnormalities; Urinalysis revealed no abnormalities; Ferritin 2447 ng/ml; IgA, IgG, IgM, complement 3, and complement 4 were basically normal; Lymphocyte subsets: CD4+ T cells 25.40%, CD8+ T cells 49.82%, CD4/CD8 ratio 0.51, CD3+CD4+ T cell count 343 cells/μl. Chest high-resolution computed tomography (HRCT) showed the peripheral zones of both lungs demonstrate increased density, manifesting as ground-glass opacities with superimposed fine reticular high-density shadows, accompanied by traction bronchiectasis (Figure 1). Initial diagnosis upon admission: Pulmonary fibrosis complicated by infection; hematological disease to be diagnosed. Bronchoscopy findings: Next-generation sequencing (NGS) of bronchoalveolar lavage fluid: *Aspergillus flavus* complex sequence count 28,738; *Aspergillus niger* sequence count 7,883; Influenza A virus (H1N1) sequence count 24,738. Cell classification of BALF: eosinophils 2.5%, NEU 92%, lymphocytes 5.5%. Folate 2.01ng/ml. Vitamin B12 253pg/ml. Final diagnosis: 1. Invasive pulmonary aspergillosis; 2. Influenza A virus infection; 3. Pulmonary interstitial fibrosis; 4. Hematological disease. Treatment: Voriconazole 200 mg iv Q12h, combined with Micafungin 150 mg iv Qd, was used to treat *Aspergillus* infection, along with Oseltamivir for antiviral therapy against influenza. After one week of treatment, the patient still had intermittent fever, so the antifungal therapy was changed to Isavuconazole. The specific regimen was: Days 1-3: Isavuconazole 200 mg iv Q12h; Days 4-9: Isavuconazole 200 mg iv Qd, followed by 200 mg orally Qd for 4 consecutive weeks. After treatment, the patient's body temperature gradually returned to normal. In the context of infection, the decrease in blood cells raised consideration of possible infection-induced

Table 1. Changes in routine blood test at different times.

Detection indicators	2025-01-14	2025-01-27	2025-09-12
RBC ($\times 10^{12}$/L)	2.14	1.97	3.10
HB (g/L)	78	72	113
HCT (%)	23.30	22.10	35.00
MCV (fl)	109	112	112.80
MCH (pg)	36.40	36.60	36.50
WBC ($\times 10^9$/L)	6.09	5.87	10.61
NEU ($\times 10^9$/L)	4.1	4.63	4.63
PLT ($\times 10^9$/L)	21	59	40

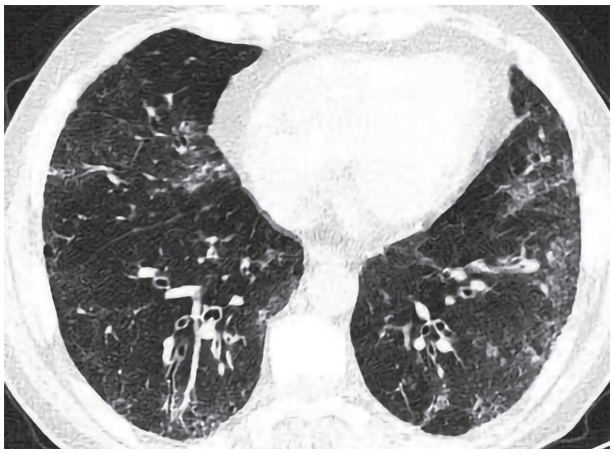

Figure 1. Chest high-resolution computed tomography (HRCT) showed the peripheral zones of both lungs demonstrate increased density, manifesting as ground-glass opacities with superimposed fine reticular high-density shadows, accompanied by traction bronchiectasis.

hemophagocytic syndrome. After anti-infection treatment, the patient's clinical symptoms improved significantly. Review of the routine blood test still shows anemia and thrombocytopenia (Table 1,2025-01-27); C-reactive protein 58.17 mg/L; Procalcitonin and IL-6 returned to normal; ferritin was 977 ng/ml. Anemia and thrombocytopenia persisted, prompting consideration of a hematological disorder; thus, bone marrow aspiration and bone marrow biopsy were performed. Bone marrow smear suggested: Poor bone marrow hyperplasia, with signs of pathological hematopoiesis and multinucleated giant cells; the presence of multinucleated giant erythrocytes could not be ruled out. Bone marrow biopsy pathology: There was extremely low proliferation of nucleated cells in the marrow cavity (<10 vol%), with reductions in all three cell lines. Lymphocytes and plasma cells were scattered and relatively easily observed, with occasional small megakaryocytes noted. No other abnormal cells or cell aggregates were identified, and there was no significant proliferation of fibrous tissue. Immunohistochemistry indicated the presence of small megakaryocytes, and cell morphology revealed pathological hematopoiesis in both erythroid and megakaryocytic lines, consistent with MDS. Bone marrow chromosome karyotype analysis: 46, XY, del (11) (q21) [1]/46, idem, add(1)(p36.3), del(5) (q13) [7]/46, XY [22]. Result description: Thirty metaphase cells were analyzed, with 8 cells showing del(11q), among which 7 had complex karyotypes (3 abnormalities). Additionally, add(1p) and del(5p) were present, indicating acquired cytogenetic variations. Antiplatelet antibody tests: Anti-GPIX antibody positive, anti-GP IIIa antibody positive, anti-GPIb antibody positive. According to World Health Organization(WHO), the International Classification of Cancer, and the 5th edition of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues [2,3], Clinical diagnosis: Myelodysplastic syndrome with low blasts.

The patient had pulmonary fibrosis. Factors such as long-term medication use in the patient's work or home environment were screened, but no specific abnormalities were identified. Physical examination of the patient revealed no abnormalities in the skin, muscle strength, or joints. Blood tests showed negative anti-neutrophil cytoplasmic antibody (ANCA). Antibody tests showed antinuclear antibody (ANA) with a nuclear granular pattern: 1:100; myositis antibody profile: anti-cNIA positive at 1:30; rheumatoid indicators showed: rheumatoid factor IgM: 70.38 RU/ml, all of which were slightly abnormal. BALF testing did not detect eosinophils, with infectious neutrophils being predominant. The patient's chest HRCT demonstrates that the lesions are predominantly distributed in the subpleural and basal regions, manifesting primarily as fine reticular opacities, accompanied by honeycombing and traction bronchiectasis. These imaging findings are consistent with the characteristic features of usual interstitial pneumonia (UIP). A multidisciplinary team (MDT) was convened to discuss the HRCT findings and other results, and according to the guidelines for idiopathic pulmonary fibrosis (update) and progressive pulmonary fibrosis in adults: Official ATS/ERS/JRS/ALAT Clinical Practice Guidelines [4], Clinical diagnosis:Idiopathic Pulmonary Fibrosis (IPF).

Given the suspicion of genetic susceptibility underlying IPF and MDS, genomic DNA from the subject was subjected to whole-exome capture and sequencing. Based on next-generation sequencing data, analyses were performed for single nucleotide variants, small fragment insertions and deletions, and large fragment copy number variations. The detection revealed variations in the BRIP1, SERPINC1,

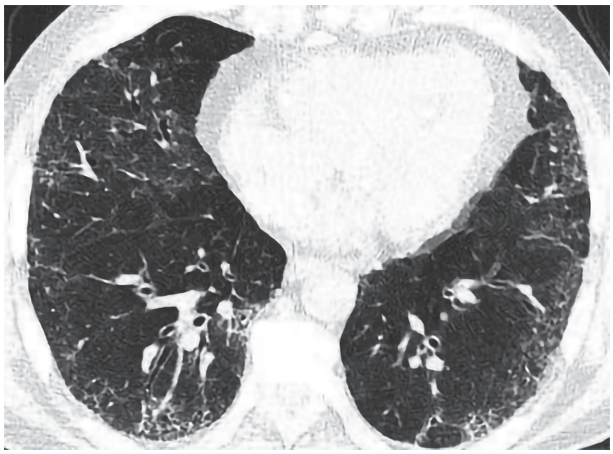

Figure 2. The post-treatment chest HRCT shows improvement in the lung's high-density areas, but there are still peripheral fine reticular shadows in both lungs, along with traction bronchiectasis.

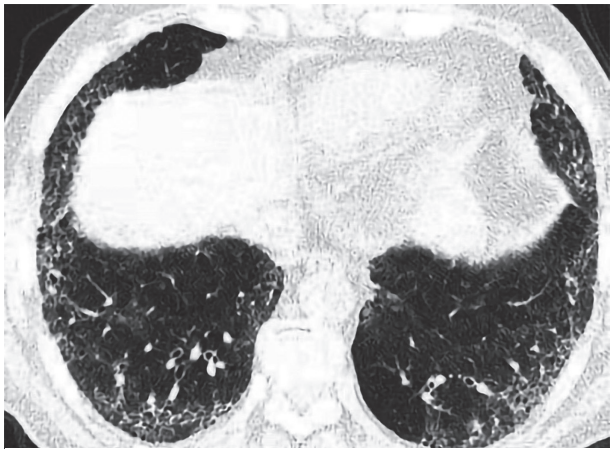

Figure 3. The post-treatment chest HRCT shows fine reticular shadows around both lower lungs, accompanied by honeycombing.

MTHFR, PCSK9, IFIH1, CPOX, NIPBL, BTNL2, BPHB4, PLEC, RBM20, KRT14, and FECH genes.

After the patient's pulmonary infection was resolved, the post-treatment chest HRCT shows still peripheral fine reticular shadows in both lungs, along with traction bronchiectasis and honeycombing (Figures 2, 3). Pirfenidone was recommended for anti-fibrotic therapy. However, the patient declined to adhere to this recommendation due to concerns regarding potential side effects. During follow-up, repeat HRCT showed a mild increase in lung reticular and honeycomb patterns.

A hematologist treated MDS with Azacitidine at a dosage of 75 mg/m² subcutaneously daily. The first course was administered for 6 days, but chemotherapy was stopped due to a lung infection. After an interval of 4 weeks, the same dosage was used for the second course, administered for 7 days. After the second chemotherapy, bone marrow suppression occurred, followed by recurrent lung infections. The patient is still receiving anti-infection treatment. Continuous follow-up over 3 months showed stable blood routine test results (Table 1, 2025-09-12).

Literature review and discussion

As early as 2003, Rosenstingl et al. [1] reported a case involving an 80-year-old female patient in whom myelodysplastic syndrome progressed to a myeloproliferative disorder accompanied by bone marrow fibrosis and pulmonary fibrosis. This case was characterized by an initial presentation of a normal karyotype and moderate fibrosis in the context of myelodysplastic syndrome, followed by the accelerated development of myeloproliferative disease and bone marrow fibrosis. In various pulmonary fibrosis models and idiopathic pulmonary fibrosis, the secretion of platelet-derived growth factor (PDGF) by alveolar macrophages and type II pneumocytes has been documented. This form of pulmonary fibrosis has been linked to an elevated concentration of PDGF in BAL. Additionally, pulmonary fibrosis has been associated with platelet storage pool diseases, such as Hermansky-Pudlak syndrome and grey platelet syndrome.

In 2009, Farris et al. [5] reported 5 cases of patients with MDS who presented with interstitial lung disease. All patients underwent video-assisted thoracoscopic surgery (VATS); biopsy revealed interstitial chronic inflammation, fibrosis, and scattered foci of alveolar injury. They concluded that cellular interstitial pneumonia with desquamative interstitial pneumonia (DIP)-like features is associated with MDS and, in some cases, heralded the development of acute leukemia. These cases exhibited substantial differences in the severity of concomitant interstitial fibrosis, and regression analysis demonstrated an inverse correlation between CD68+ macrophages and the degree of fibrosis.

Himmelmann et al. [6] in 2021 and Beecher et al. [7] in 2024, each reported a case of a patient diagnosed with VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome through genetic testing. A 77-year-old male patient had inflammatory processes such as Sweet's syndrome of the skin, pulmonary fibrosis, as well as the development of macrocytic anaemia with vacuolization of myeloid and erythroid precursors [6]. A 68-year-old male patient presented with eyelid swelling, edema, and enlarged lacrimal glands, accompanied by intermittent episodes of angioedema-like lesions on the face and limbs, recurrent jaw pain, rashes, progressive pulmonary fibrosis, and MDS [7]. VEXAS syndrome, a newly delineated late-onset acquired autoinflammatory disorder stemming from mutations in the UBA1 gene, exhibits a broad spectrum of clinical manifestations that can be broadly categorized into inflammatory and hematologic lesions[8]. These two cases underscore the possibility that individuals with VEXAS may develop pulmonary fibrosis, potentially precipitated by systemic inflammation and other contributory factors.

In recent years, telomeropathies have been considered to be possibly related to the simultaneous presence of both. In 2022, Doubkova [9] reported a case of a 69-year-old white male suffering from both MDS and pulmonary fibrosis. Given whole exome sequencing revealed a germline heterozygous variant of CTC1 gene (c.1360delG). This type of 'frame-shift' mutation leads to premature stop codons and results in the occurrence of telomeropathies. So far, this gene variant has been described in a heterozygous state in adult patients with hematological diseases such as idiopathic aplastic anemia or paroxysmal nocturnal hemoglobinuria, but also in interstitial pulmonary fibrosis. In 2025, Watanabe [10] reported a case of a 40-year-old male with Dyskeratosis congenita (DC), characterized by a mucocutaneous triad complicated by pulmonary fibrosis and MDS. DC is a rare genetic disorder that is caused by abnormal telomere shortening. The telomere length of lymphocytes was extremely short (-3.3 standard deviations). Telomeropathies are closely associated with premature aging and a reduction of cell ability to cope with recurrent damage. Several pulmonary, hematological, or liver diseases are associated with telomeropathies. These diseases include pulmonary fibrosis as IPF and MDS.

As evident from the aforementioned literature, extensive research has been conducted on the correlation between these two diseases. In recent years, exome sequencing has gradually been integrated into clinical practice, enabling feasible investigations at the genetic level. In our reported cases, no mutations were detected in telomere disease-related genes or VEXAS-associated genes; however, several genes with abnormal expression were identified. Upon examining these genes, we found three variants that may contribute to the co-occurrence of both diseases (Table 2: Details of the variant identified in this case):

- c.665C>T(p.Ala222Val) variant of MTHFR gene shown in (Figure 4A);
- c.1954A>G(p.Asn652Asp) variant of PCSK9 gene shown in (Figure 4B);
- c.2616+3A>G variant of the IFIH1 gene shown in (Figure 4C).

The enzyme encoded by the MTHFR (methylenetetrahydrofolate reductase) gene is a key enzyme in folate (vitamin B9) metabolism, catalyzing the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. The activity of the MTHFR enzyme directly influences the level of homocysteine in the blood. Folate metabolism is critical for the synthesis of nucleotides. Danjou et al. [11] used an ImmunoChip to genotype 133 cases of MDS and 3,894

Table 2. Details of the variant identified in this case.

Gene	Chromosome	Position	Reference sequence	DNA Change	Amino acid change	Zygosity	Annotation	dbSNP157	ACMG classification
MTHFR	1	11856378	NM_005957.5	c.665C>T	p.Ala222Val	Heterozygous	missense	rs1801133	Likely pathogenic
PCSK9	1	55529132	NM_174936.4	c.1954A>G	p.Asn652Asp	Heterozygous	missense	rs201280059	VUS
IFIH1	2	163128733	NM_022168.4	c.2616+3A>G	P.?	Heterozygous	intron	rs1417711279	VUS

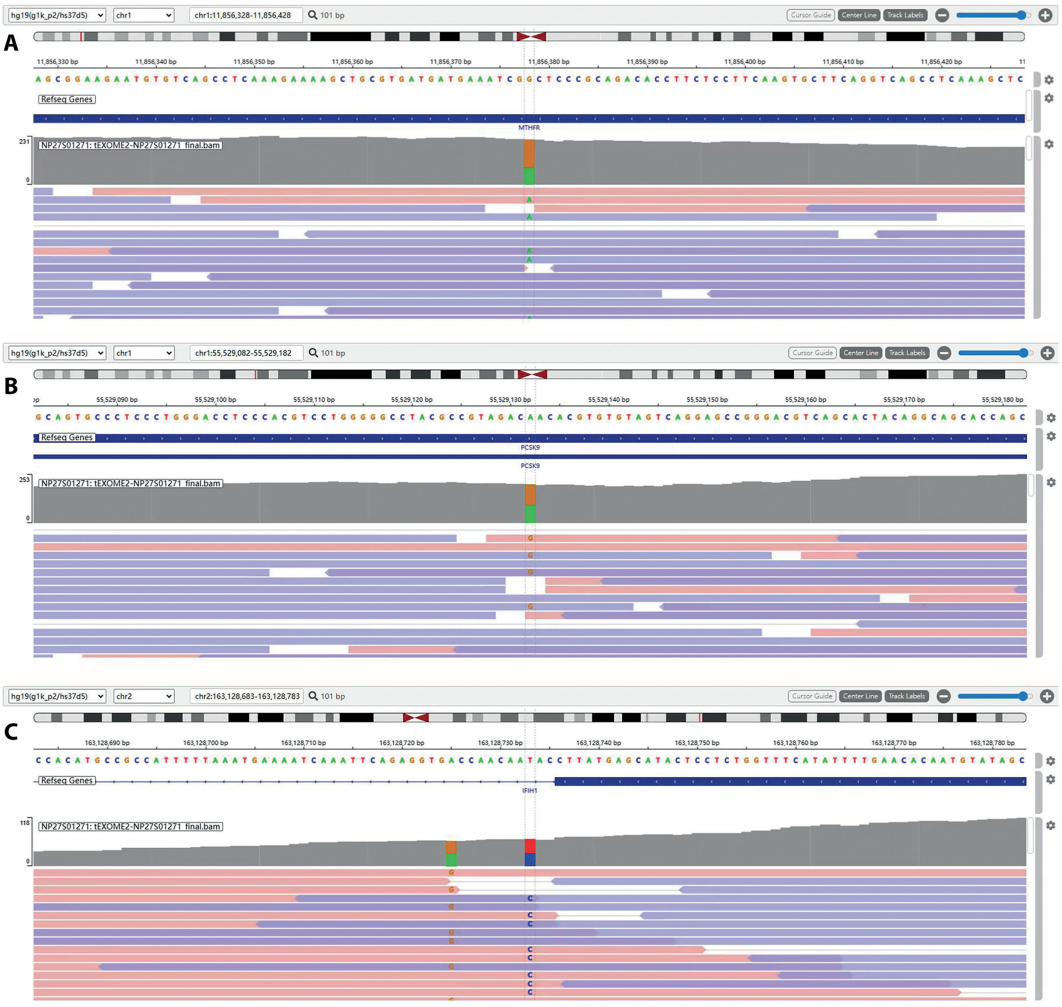

Figure 4. Integrative Genomics Viewer (IGV) image of three variants in a Chinese patient. The result of c.665C>T(p.Ala222Val) variant of MTHFR gene shown in (A), the c.1954A>G(p.Asn652Asp) variant of PCSK9 gene shown in (B), and the c.2616+3A>G variant of the IFIH1 gene shown in (C).

controls, identifying a mutation in the MTHFR gene on chromosome 20 at rs71325459 ($p = 1.16 \times 10(-12)$). MTHFR can reduce the misincorporation of uracil into DNA, which would otherwise potentially lead to double-strand breaks during the uracil excision repair process. In hematologic malignancies, different MTHFR gene SNP sites, particularly rs1801133, are associated with the risk of childhood acute lymphoblastic leukemia, lymphoma, and secondary myeloid malignancies. Visani [12] performed genetic polymorphism tests on 108 MDS patients and found that the MTHFR 677T/T genotype was associated with short-term survival, irrespective of azacitidine treatment administration. Research by Nzabarushimana et al. [13] revealed that exposure to high levels of iron induced pulmonary fibrosis in mice, with significant hypermethylation of MTHFR, Cadm1, Cdh13, Cdkn1c, and Sfrp1 observed in epigenetic changes.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is one of the major regulators of low-density lipoprotein receptor (LDLR), and stimulated cells induce proinflammatory cytokines. Genes which involved in the biosynthetic and metabolic processes of cholesterol, include FSCK9, are differential genes of IPF [14]. Different animal experiments have confirmed that, PCSK9 plays a crucial role in the progression of PF-induced PH by regulating cell EMT and Wnt/beta-catenin signaling. Targeting PCSK9 expression

or activity could effectively control lung fibrosis and its PH complication, Lipid-lowering treatment has the potential to alleviate obesity-induced airway hyperresponsiveness and lung fibrosis by inhibiting the NLRP3 inflammasome, RAS and cholecystokinin activity [15, 16]. 5-azacytidine (5-AzaC), have been shown to lower malignant progression to acute myeloid leukemia and to prolong survival in patients with MDS, the research of Poirier et al. [17] show that 5-AzaC selectively and very potently reduces expression of key genes involved in cholesterol and lipid metabolism (e.g. PCSK9, HMGCR, and FASN) in all tested cell lines and *in vivo* in mouse liver. 5-AzaC disturbs cholesterol and lipid homeostasis, probably through the glycerolipid biosynthesis pathway, which may contribute mechanistically to its beneficial cytostatic properties.

Tuerxun [18] integrated the GSE4619, GSE19429, GSE30195, and GSE58831 microarray datasets of CD34+ cells to identify differentially expressed genes (DEGs) in MDS. They identified significant hub genes, including 168 upregulated hub genes, among which Interferon Induced with Helicase C Domain 1 (IFIH1) was one. In a retrospective observational study [19], transcriptomics was used to compare gene expression patterns in COVID-19 with those in autoimmune lung diseases and IPF. The results showed strong induction of IFIH1 in COVID-19 and autoimmune interstitial lung disease (ILD), and IFIH1 strongly correlated with an IL-15-centric type-1 interferon response and an activated CD8+ T cell signature, which is an immunologic hallmark of progressive ILD in the context of systemic autoimmune rheumatic diseases.

In summary, although MTHFR, PCSK9, and IFIH1 are not widely recognized as susceptibility genes for MDS and pulmonary fibrosis, literature reports suggest that variations in these genes may increase the risk of developing these two conditions.

The question of whether the combination of MDS and pulmonary fibrosis is accidental or inevitable remains a subject of ongoing investigation. Current evidence, as synthesized in this case report and associated literature review, suggests that their co-occurrence is unlikely to be purely coincidental.

Several lines of reasoning support this perspective. First, multiple case reports have documented an association between MDS and interstitial lung disease, including pulmonary fibrosis, with specific histological patterns and immunological signatures observed in affected patients. Second, genetic explorations have identified mutations in genes such as CTC1, MTHFR, IFIH1, and PCSK9 that are linked to both conditions, pointing to potential shared pathogenic mechanisms at the molecular level. These genes are involved in critical pathways like telomeropathies, folate metabolism, immune regulation, and inflammatory responses, which could contribute to the development of both hematological and pulmonary manifestations.

However, in the present case, only the patient solely underwent whole-exome sequencing, and no genetic testing was conducted on other family members. Consequently, the hereditary origin of the aforementioned variants remains undetermined—specifically, it is not possible to confirm whether these variants are *de novo*, somatic, or germline in nature. So the precise nature of this relationship—whether it is inevitable due to inherent genetic or biological connections—has not yet been definitively established. According to the above cases and literature reports, the coexistence maybe arise from a complex interplay of multiple genetic mutations, environmental triggers, and dysregulated immune processes, rather than a single deterministic factor.

A major limitation of this study is the paucity of genetic testing results in the majority of cases, coupled with the absence of systematic familial genetic follow-up. This precludes a comprehensive evaluation of the potential genetic contributions to the observed disease associations.Further research is needed, using case-control or cross-sectional studies combined with genetic testing, to determine whether their co-occurrence is driven by inevitable biological links or facilitated by other factors, and to clarify the mechanism.

Conclusion

MTHFR, IFIH1, PCSK9 and CTC1 are involved in key pathways including folate metabolism, immune regulation, inflammatory responses and telomere disorders, which may contribute to the pathogenesis of both MDS and pulmonary fibrosis. The coexistence of these two conditions is likely attributed to complex interactions among multiple gene mutations, environmental triggers, and dysregulated immune processes, rather than a single determinant.

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