

IGG4-RELATED DISEASE: A CLINICAL CASE REPORT

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Abstract. Immunoglobulin G4-related disease (IgG4-RD) is a systemic disease affecting one or more organs. Pathomorphologically, a dense infiltrate of lymphocytes and IgG4 plasmacytes, and subsequent fibrosis are detected. Despite the many hypotheses of genetic predisposition, molecular mimicry and autoimmune nature of the disease, the etiology still remains unclear. Both innate and acquired immunity are believed to play a key role in disease pathogenesis. The involvement of occupational risk factors is also discussed. The possible involvement of multiple organs and systems (most often lacrimal and salivary glands, kidneys, lungs, aorta, pancreas, hepatobiliary duct, lymph nodes, as well as retroperitoneal fibrosis) is the reason for the multidisciplinary approach in this disease. In pulmonary involvement, clinical manifestations are nonspecific (cough, dyspnea, chest or back pain, hemoptysis, low-grade fever, weight loss) or patients are asymptomatic, and pulmonary changes are an incidental finding on imaging. Up to 60% of cases of autoimmune pancreatitis represent a pancreatic manifestation of IgG4-related disease, with the majority of patients being elderly men. The most common differential diagnosis is a malignant process due to the tumor-like changes of the affected organ. Treatment with corticosteroids, immunosuppressors and symptomatic agents in most cases has a good effect, although relapses of the disease are also observed. We present a clinical case of a 72-year-old patient whose first complaints were nonspecific, for which a chest computed tomography was performed with visualization of four solid nodules in the right lung. After antibiotic therapy, without effect and deterioration of the patient's condition, video-assisted thoracoscopy, biopsy, histology and immunohistochemistry were performed. A diagnosis of IgG4-RD with pleural and lung involvement was confirmed. Anemic syndrome, increased values of amylase, lipase, and acute phase parameters were found from the laboratory tests. Through endoscopic retrograde cholangio-pancreatography, autoimmune pancreatitis was diagnosed in the course of IgG4-RD. A plastic stent was placed on the common bile duct. Treatment with Prednisolone 40 mg/day was started with a subsequent dose reduction. Follow-up computed tomography of the lung after 9 months demonstrated a reduction of the described changes in the lungs, but with persistent lymphadenopathy and fibrotic changes. Azathioprine 100 mg daily was added to prednisone therapy. Against the background of the combined treatment, an improvement of the clinical condition and laboratory parameters was established.

Key words: immunoglobulin G4-related disease, clinical case

INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a systemic disease presenting with tumor-like changes in one or more organs, caused by tissue infiltration of IgG4 plasma cells, serum IgG4 level above 1.35 g/l and subsequent fibrosis [1, 2, 3, 4, 5, 6, 7].

Pathomorphologically, a dense infiltrate of lymphocytes and IgG4 plasma cells, fibrosis and obliterating phlebitis were detected [1, 3, 6]. The etiology remains unclear, although it has been linked to genetic origin, bacterial infection, molecular mimicry, and autoimmune disorders [5]. Some genetic susceptibility factors (human leukocyte antigen (HLA) haplotypes as well as non-HLA genes) have

been identified [3, 6]. Although both innate and acquired immunity are key in the pathogenesis of the disease, the mechanisms in IgG4-RD remain largely unclear. Patients with IgG4-RD show a predominant infiltration of M2 macrophages (alternatively activated) in multiple tissues, incl. pancreas, pleura, parotid, lacrimal and salivary glands. These macrophages activate T2 helper lymphocytes (Th2) and subsequent fibrosis through the production of profibrotic cytokines (IL-10, IL-33) and chemokines (cc-chemokine ligand 18, CCL18). Mast cells, which show strong cytoplasmic staining for IgE, are increased in patients with IgG4-RD. These cells have a key role in both chronic inflammation and many autoimmune diseases. They are activated by various biological substances and secrete media-

tors, including Th2 and regulatory cytokines, which also contribute to fibrosis. Activated basophils (which under normal circumstances are less than 1% in peripheral blood) can also lead to the differentiation of inflammatory monocytes into M2 macrophages, influence the Th2 immune milieu (produce 10-fold higher levels of Th2 cytokines such as IL-4 and IL-13) and affect the production of IgG4 cells [4, 8, 9]. Although the role of complement in the pathogenesis of IgG4-RD is controversial, C3 and C4 fractions of complement have been reported to be reduced (hypocomplementemia) in 36% of patients with IgG4-related autoimmune pancreatitis [4]. In the affected tissues or organs of IgG4-RD patients, Th2 secreted cytokines such as IL-4, IL-5, IL-13 and T regulatory cytokines such as IL-10 and TGF- β are significantly increased. Compared with healthy controls, in the peripheral blood of IgG4-RD patients, memory B cells are increased, while regulatory B cells are decreased; expression of CD 80 and CD 86 on peripheral CD19+ B cells is increased [4]. These B cells reach the inflamed tissues, differentiate and proliferate into IgG4 cells [8]. Currently, serum IgG4 is the most important biomarker for diagnosis and monitoring response to treatment. In normal blood, IgG4 represents only 1-7% of IgG, but in patients with IgG4-RD its level is significantly increased. By binding to circulating allergens, IgG4 inhibits IgE binding to them, thereby reducing mast cell activation and inhibiting Th2 cell-mediated immune responses. However, the role of all these cells in the pathogenesis of the disease needs to be further investigated [4]. A Dutch study reported occupational risk factors (exposure to solvents, oils, pigment paints, industrial and metal dust) associated with IgG4-RD [10].

The possible involvement of multiple organs and systems is the reason for the multidisciplinary approach in this disease. Among the most frequent pathological findings are deviations in the function of the lacrimal and salivary glands, kidneys, lungs, aorta, pancreas, hepatobiliary duct, lymph nodes, as well as retroperitoneal fibrosis [1, 2, 4, 5, 6, 7, 11, 12].

Initially, clinical manifestations of pulmonary involvement are nonspecific and most commonly include cough, shortness of breath, chest or back pain, hemoptysis, low-grade fever, weight loss [2, 3, 8, 12, 13, 14]. Patients may be asymptomatic, and lung changes (nodules, lymphadenopathy, septal thickening and fibrosis) can be detected on imaging of the chest as an incidental finding [2, 3, 12, 14].

Up to 60% of cases of autoimmune pancreatitis represent a pancreatic manifestation of IgG4-related sclerosing disease. The majority of patients are elderly (60-65 years old) men (70-80%) [3, 15]. More than half of those diagnosed with autoimmune pancreatitis have lung lesions [14], with hilar lymphadenopathy being the most common extrapancreatic lesion (80.4%) [16]. In terms of differential diagnosis, the most common diagnosis is a malignant process [2, 5, 6, 8, 11, 13].

Treatment is mainly with corticosteroids, immunosuppressors and symptomatic agents [1, 2, 3, 5, 6, 7, 8, 11, 12, 13, 16, 17, 18]. Relapses of the disease are possible [2, 5, 6, 7, 12], necessitating timely medical treatment and/or surgical intervention [2, 6].

CLINICAL CASE DESCRIPTION

We present a clinical case of a 72-year-old Caucasian patient whose first complaints were registered in October 2022. The patient reported general weakness, fatigue, polyarthralgias, polymyalgias, for which a computed tomography (CT) of the chest was performed with a conclusion of presence of four solid nodules in the right lung (Figure 1). Antibiotic therapy was administered and follow-up was recommended.

Three months later, on the occasion of severe pain in the right inguinal fold, the lower back and the anterior surface of the right thigh, a magnetic resonance of the lumbar vertebrae and the hip joint was performed, which showed degenerative changes at multiple levels, relative stenosis of the spinal canal at the level L3-L4 and root compression more to the right.

In March 2023, a controlled CT scan of the chest and abdomen was performed (Figure 2), which visualized mediastinal hilar lymphadenopathy, a small pleural effusion on the right, thickened costal and visceral pleurae bilaterally, and thickened interstitial septa in the 3rd segment in right and in the 1st and 6th segments bilaterally. New oval nodules are found in the lung (Figure 2). An oval hypodense lesion and edema in the surrounding adipose tissue are seen in the tail of the pancreas. An adenoma was found in the right adrenal gland.

After video-assisted thoracoscopy (VATS), biopsy, histology, and immunohistochemistry, a diagnosis of IgG4-RD involving the pleura and lung was accepted. Diagnoses of mesothelioma, lymphoproliferative disease, and tuberculosis were ruled out (negative test based on the release of interferon – gamma – in the case of QuantiFERON TB Gold). Due to worsening of the condition and pronounced pain symptoms

in the epigastrium area, radiating to the left and right lower ribs, back to the waist and elevated values of amylase, lipase, acute phase parameters, an endoscopic retrograde cholangio-pancreatography (ERCP) was performed. Autoimmune pancreatitis was diagnosed in the context of IgG4-RD. A plastic prosthesis of the choledochus duct was placed. Treatment with prednisolone 40 mg daily with subsequent dose reduction was initiated. The patient has weight loss – about 10 kg for half a year. The laboratory tests also revealed an anemic syndrome (table 1 and table 2).

After 9 months, a follow-up CT scan of the chest was performed, which revealed a reduction of the described changes compared to the previous examination with reverse development of pleural effusions and lung nodules, less pronounced thickening of the pleura, reduced lymph nodes. However, mediastinal and hilar lymphadenopathy persisted, and fibrous changes in the lung parenchyma, more pronounced on the right (Figure 3).

Treatment with azathioprine 100 mg daily was assigned to prednisone therapy. Improved laboratory indicators were observed after one month of treatment with azathioprine (Table 3).

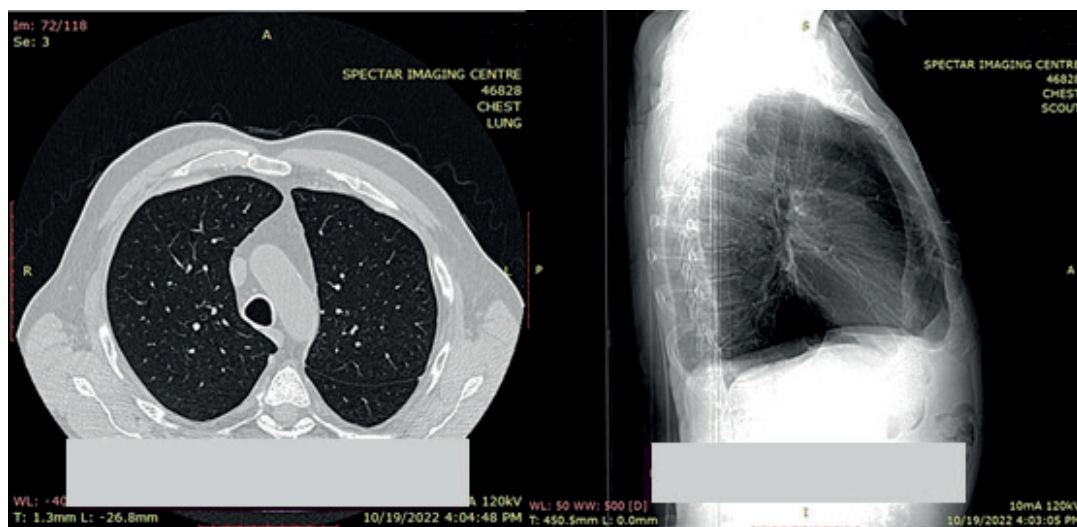


Fig. 1. Baseline computed tomography. Four solid nodules between 5 and 10 mm are visualized in the right lung

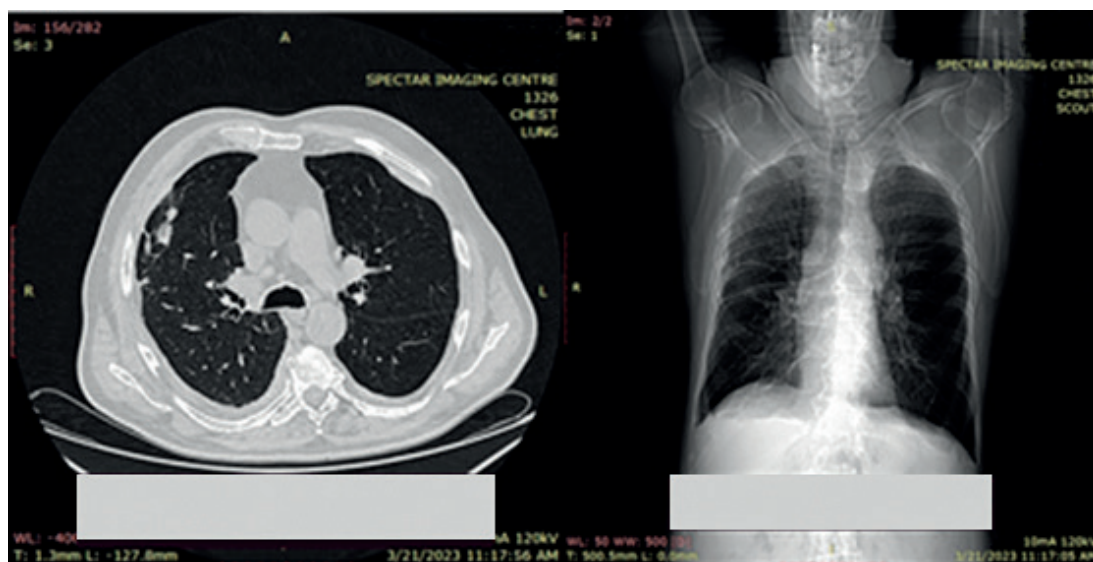


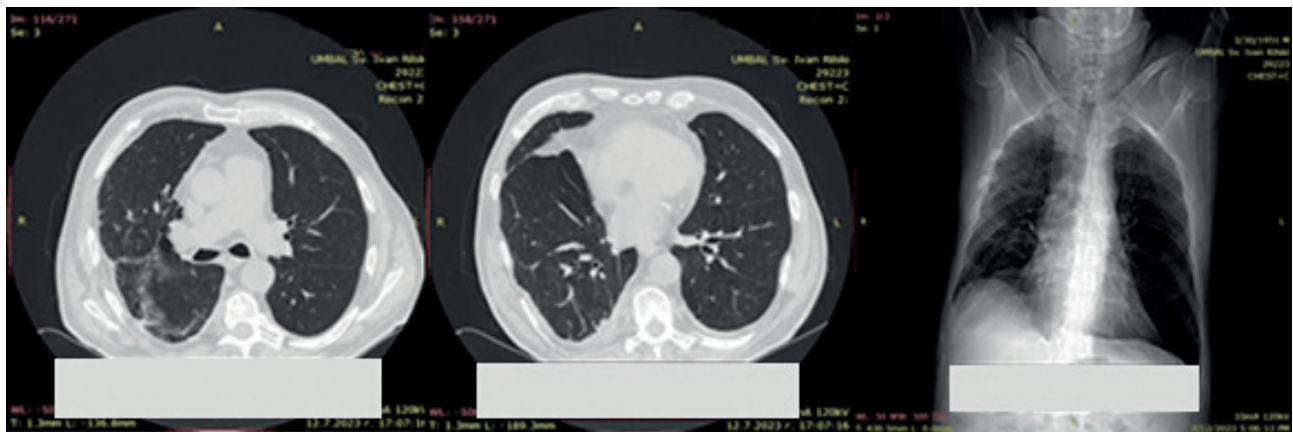
Fig. 2. Follow-up computed tomography after 5 months. A small pleural effusion, lymphadenopathy bilaterally, pleural thickening bilaterally, new oval nodules bilaterally are noted on the right. The initial conclusion is that the described changes are probably due to a disseminated malignant process involving the pleura, the lung and the tail of the pancreas

Table 1. Laboratory tests from July 11, 2023

Name	Results	Unit	Lower limit	Upper limit
WBC	10.10	$\times 10^9/L$	3.50	10.50
RBC	4.70	$\times 10^{12}/L$	3.70	5.90
HGB	117	g/L	120.00	180.00
HTC	0.365	L/L	0.36	0.53
MCV	77.6	fL	80.00	96.00
MCH	24.9	pg	27.00	33.00
MCHC	321	g/L	300.00	360.00
PLT	200	$\times 10^9/L$	130.00	360.00
LYM%	18.1	%	20.00	48.00
MONO%	5.8	%	1.00	11.00
EO%	0.4	%	0	6.50
BASO%	0.1	%	0	2.00
NEUT%	75.1	%	40.00	70.00
LYM#	1.84	$\times 10^9/L$	1.00	4.00
MONO#	0.58	$\times 10^9/L$	0	0.80
EO#	0.04	$\times 10^9/L$	0	0.50
BASO#	0.01	$\times 10^9/L$	0	0.14
NEUT#	7.62	$\times 10^9/L$	2.00	7.00
RDW	17.30			
MPV	10.8	fL	6.10	12.50
Glucose	7.87	mmol/L	3.50	6.70
Amylase	149.93	U/L	0	90.00
Lipase	147.13	U/L	0	67.00
CRP/C-reactive protein	7.80			<6
pH urine	5.5			
Specific Gravity	1.014			
Protein (in urine)	negative (-)			
Glucose (in urine)	negative (-)			
Ketones (in urine)	borderline (+-)			
Urobilinogen (in urine)	unenlarged			
Bilirubin (in urine)	negative (-)			
Blood (in urine)	negative (-)			
Nitrites (in urine)	negative (-)			
Leucocytes (in urine)	positive (+)			
Ery	0			
Leu	3.3			up to 3
Epithelial cells	0			
Casts	0			
Crystals	0			
Bacteria	0			

Table 2. Immunological results from July 12, 2023

Name	Results
Rheumatoid factor (RF)	< 30
Anti-nRNP/Sm	1
Anti-Sm	0
Anti-ssA	1
Anti-Ro-52	0
Anti-ssB	0
Anti-Scl-70	1
Anti-PM-Scl	1
Anti-Jo-1	2
Anti-Cent.-B	2
Anti-PCNA	1
Anti-dsDNA	0
Anti-Nucleosomes	0
Anti-Histones	0
Anti-Rib-P	0
Anti-M 2	2
Anti-DFS70	0
AMA-M2	0
Anti-PR3	2.40
Anti-MPO	0.70
ANA - IIF screening (HEp-2 cells)	(-) negative

**Fig. 3. Follow-up computed tomography 9 months after baseline. A reduction of the lung nodules, a less pronounced thickening of the pleura, reduced lymph nodes were found. Fibrous changes persist****Table 3. Laboratory indicators after one month of treatment with azathioprine**

Name	Results	Unit	Referent range
Erythrocyte sedimentation rate	33	mm/h	Up to 37
WBC	9.84	$\times 10^9/L$	3.50-10.50
LYM%	17.8%		20.0-48.0
MONO%	7.0%		1.0-11.0
EO%	0.6%		Up to 6.5
BASO%	0.7%		Up to 2.0
NEUT%	73.9%		40.0-70.0
LYM#	1.750	$\times 10^9/L$	1.000-4.000
MONO#	0.690	$\times 10^9/L$	Up to 0.800
EO#	0.060	$\times 10^9/L$	Up to 0.500
BASO#	0.070	$\times 10^9/L$	Up to 0.140
NEUT#	7.270	$\times 10^9/L$	2.000-7.000

Continuation tabl. 3

RBC	4.63	$\times 10^{12}/L$	4.40-5.90
HGB	122	g/L	135-180
HTC	0.387	L/L	0.400-0.530
MCV	83.6	fL	80.0-96.0
MCH	26.3	pg	27.0-33.0
MCHC	315	g/L	300-360
RDW	15.4 %		11.5-14.5
PLT	223	$\times 10^9/L$	130-440
MPV	9.9	fL	6.1-13.5
Pct	2.20	ml/L	1.00-4.80
PDW	11.9	fL	8.0-23.0
Creatinine	111	$\mu\text{mol}/L$	Up to 104.00
Urea	10.40	mmol/L	3.00-11.90
Uric acid	301.00	$\mu\text{mol}/L$	200.00-420.00
Bilirubin (total)	3.50	$\mu\text{mol}/L$	Up to 21.00
Bilirubin – direct	1.90	$\mu\text{mol}/L$	Up to 6.50
ASAT	11.90	U/L	Up to 40.00
ALAT	18.40	U/L	Up to 41.00
GGTP	47.00	U/L	Up to 60.00
Alpha amylase	111.00	U/L	Up to 100.00
Lipase	70.00	U/L	Up to 60.00
Creatine phosphokinase	43.00	U/L	Up to 190.00

DISCUSSION

IgG4-RD is a rare disease for which a limited number of publications are found in the scientific literature [2, 5, 6, 11, 12, 13, 19]. Liu J et al. describe a retrospective study of 10 patients (male:female ratio = 9:1) with a mean age of 59.7 years with confirmed IgG4-RD. Clinical manifestations are nonspecific, with cough being the most common symptom (4/10), followed by chest or back pain (2/10), hemoptysis (2/10), low-grade fever (1/10), and ocular symptoms (1/10). Three patients were asymptomatic and were incidentally identified with pulmonary changes on chest radiography. The majority of patients (80%) had multiple organ involvement, most commonly mediastinal lymph nodes (70%), nasal sinus (30%), lacrimal glands (10%), parotid gland (10%), submandibular salivary gland (10%) and pituitary gland (10%). In the patients, increased levels of serum IgG4 (in 6 patients), increased acute phase parameters were detected. Large pulmonary nodules were present in 5 patients, while numerous diffusely located small nodules were found in all [2]. Most of the patients had bilateral lung involvement. All had abundant lymphoplasmacytic cell infiltration and fibrosis. Tumor markers – carcinoembryonic

antigen and CA-125, were within reference limits. Seven patients were treated with glucocorticoids: five on prednisone monotherapy and two on combined treatment with prednisone and cyclophosphamide. Two patients underwent lung surgery, and one patient with a mild course of the disease received only symptomatic treatment. Clinical improvement occurred in all patients. In 6 patients, there was a reduction of the lung lesions detected by CT, and in two, no change in the size of the lung nodules was recorded. Two patients had relapse and new lung nodules, but after a repeated course of treatment with prednisone and immunosuppressive drugs, they recovered completely [2].

Another group of authors – Vargas C and colleagues, present a clinical case of a 63-year-old man, a smoker, with complaints of cough, dyspnea and weight loss (13 kg in 1 year). Physical examination revealed enlarged inguinal and cervical lymph nodes. A CT scan visualized cervical, mediastinal, hilar, axillary, retroperitoneal and iliac lymphadenopathy. Generalized, smooth, and uniform thickening of the interlobular septa was observed throughout the lung parenchyma [13]. Blood tests show an increase in serum immunoglobulins. Biopsies of lung tissue and cervical lymph nodes

were performed, and the histological result confirmed the presence of multiple positive IgG4 plasma cells and strongly ruled out malignancy. The patient was treated with corticosteroid therapy with prednisone 60 mg/day with good therapeutic effect. Two months after treatment, a CT scan showed a significant reduction in changes in the right lobe, with significantly less interstitial involvement [13]. A case of a 63-year-old man with autoimmune pancreatitis whose chest CT showed ground-glass and honeycomb changes, predominantly in the lower lobes, and transbronchial lung biopsy demonstrated interstitial infiltration by lymphocytes and IgG4-positive plasma cells has been reported [17]. In the differential diagnosis of these patients, the following are discussed: malignant lymphoproliferative process with lymphangitic carcinomatosis of the lung, Castleman's disease, primary lung malignancy, sarcoidosis.

Corroborating the literature, Duvic et al. described a 38-year-old man with autoimmune pancreatitis, retroperitoneal fibrosis, and multiple nodular lesions in the lung. The serum IgG4 level was elevated, and a lung biopsy showed histopathological features of organizing pneumonia [18]. The patient was treated effectively with oral prednisone, with a significant reduction in pulmonary infiltrates subsequently recorded [17, 18].

In another retrospective study that reviewed imaging studies of 90 patients with autoimmune pancreatitis, 54% of patients were noted to have lung lesions. Contrast-enhanced CT was performed in 69 patients, in which 54 (78%) patients were found to have hilar lymphadenopathy [14]. Respiratory symptoms (cough, dyspnea on exertion, and chest pain) were described in approximately half of the patients, while the remainder had abnormal intrathoracic imaging findings in the absence of respiratory symptoms [3, 14]. In a study of 65 patients with autoimmune pancreatitis, Hamano et al. reported that hilar lymphadenopathy detected by CT and gallium-67 scintigraphy was the most common extrapancreatic lesion (80.4%) [16]. According to Campbell SN et al. pulmonary manifestations in IgG4 are nonspecific and may include cough, dyspnea, fever, and chest pain [8].

CONCLUSION

IgG4-RD is a systemic disease involving multiple organs and systems with diverse clinical symptoms and a wide differential diagnosis. The clinical case, presented by us, of a man with IgG4-RD involving the

pleura and lung and autoimmune pancreatitis developed as a disease manifestation is consistent with the reported cases in the scientific literature. After treatment with prednisolone and azathioprine, the patient experienced clinical improvement, normalization of laboratory parameters and reverse development of lung changes. Monitoring and timely treatment of relapses in patients with IgG4-RD is a key approach to prevent complications and improve their quality of life.

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