Case Report

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TANAFFOS

IgG4-Related Lung Disease in a Patient with Chronic Granulomatous Disease: A Case Report

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Background: IgG4-related disease may initially present with pulmonary pseudotumor, making the diagnosis challenging particularly in patients prone to granulomatous inflammation. Here, we describe the first case of chronic granulomatous disease with associated lung IgG4RD.

Case Presentation: An 8.5-year-old male was hospitalized two years ago with exertional dyspnea, mild cough, chest pain, and nocturnal sweating and was found to have a tumor-like mass in the right lung. The histopathologic findings were consistent with extensive peripheral fibrosis and infiltration of mixed inflammatory cells without any evidence of acid-fast bacilli/fungal elements. Treatment with prednisolone resulted in considerable symptom resolution. Following the discontinuation of prednisolone by the patient, symptoms recurred, gradually exacerbated, and he developed anorexia and weight loss. The next chest spiral computed tomography (CT) scan showed a larger mass in the right lung, right lung collapse, and mediastinal metastasis. The abdominal ultrasound and CT scan were normal. In laboratory evaluation, low counts of B and T cells, normal natural killer cells, high levels of IgG4, and high inflammatory markers were detected. The nitro blue tetrazolium test was zero in two consecutive evaluations. In virtue of high IgG4 level, organ-specific mass, notable tissue fibrosis, and mixed inflammatory cell infiltrate, he was diagnosed with concurrent CGD and IgG4RD, but progressed to respiratory failure and died despite the reinstitution of steroid therapy.

Conclusion: The overlap between inborn errors of immunity and IgG4RD is not common. Further studies to investigate IgG subsets among IEI patients can help elucidate clinicopathological correlations between these two immune-mediated disorders.

Keywords: IgG4-related disease; Chronic granulomatous disease; Pulmonary; Inborn errors of immunity

INTRODUCTION

Inborn errors of immunity (IEIs), formerly called primary immunodeficiency disorders (PIDs), are inherited disorders of the immune system with a vast spectrum of clinical presentations including recurrent infections, allergy, autoimmune/autoinflammatory disorders, and malignancy (1). Chronic granulomatous disease (CGD) is a subgroup of IEIs with inherited defects in the phagocytes,

resulting from mutations in the components of the NADPH oxidase complex, reduced or absent oxygen radical synthesis, and impaired killing of intracellular bacteria and fungi (2). CGD patients typically present with recurrent life-threatening infections and granulomatous inflammatory responses in multiple organs, particularly the lungs (3). It is estimated that pneumonia and chronic pulmonary disorders complicate more than half of CGD patients and are the major reasons for hospitalization (4, 5). The chronic inflammatory response may show up as granuloma formation and pulmonary fibrosis, particularly in long-term disease (6, 7). Most pulmonary masses identified in patients with CGD originate from the granulomatous nature of the disease; however, other etiologies may underpin a mass-related obstructive airway disease including lung malignancies, fungal infections, and infiltrative disorders that are often undistinguishable via imaging. (8).

IgG4-related disease (IgG4RD) is a systemic inflammatory disorder, characterized by infiltration of $IgG4^+$ plasma cells in different tissues, fibrotic change, and often elevated serum IgG4 (9). The pattern of organ involvement seems to change with age, with the lacrimal gland and sinus involved more frequently at lower ages and internal organs (such as lungs, pancreas, biliary tract, retroperitoneal tissue, and prostate) infiltrated at higher ages (10). Pulmonary involvement of IgG4RD may be asymptomatic or mild at presentation and include hilar or mediastinal lymphadenopathies, nodules, bronchiectasis, pleural disorders, and neoplasia or interstitial lung disease mimicker lesions (11, 12). The latter is clinically important in the differential diagnosis of lung mass, particularly in patients with immunologic abnormalities.

There are few studies in the literature reporting patients with both pediatric IgG4-RD and IEIs and the association between these two immune-mediated disorders is barely understood. The diagnosis of IgG4RD in pediatric patients is challenging and the presence of an underlying CGD adds to the complexity of the diagnosis, given their similar lung involvement and rare prevalence in the general population.

Herein, we presented the first report on pediatric IgG4RD in chronic granulomatous disease (CGD) to broaden the spectrum of their clinical pictures and facilitate the diagnosis and management of similar patients.

CASE SUMMARIES

An 8.5-year-old male presented with complaints of dyspnea. He was the third child of non-consanguineous parents and the family history was unremarkable.

He was hospitalized two years ago with exertional dyspnea, mild cough, chest pain, and nocturnal sweating and was found to have a tumor-like mass in the right lung (Figure 1 A). In the chest magnetic resonance imaging (MRI) obtained at the last admission, the mass had a diameter of 52*15*61 millimeters with invasion to atria, completely obstructing the right upper lobe bronchus and both right pulmonary veins.

The initial histopathologic examination of the mass showed fibrovascular tissue with the infiltration of mixed inflammatory cells. Three weeks later, the second evaluation of the same sample in another center was consistent with non-necrotizing granulomatous inflammation, central neutrophilic micro-abscess, and extensive peripheral fibrosis without any evidence of acid-fast bacilli or fungal elements (Figure 2 A, B).

Treatment with 1.5 mg/kg of prednisolone for two months and then a maintenance dose of prednisolone (0.5 mg/kg) for nine months resulted in considerable symptom resolution. The follow-up chest X-ray (CXR) showed a reduction in the size of the mass. After 15 months, following the discontinuation of prednisolone by the patient, symptoms recurred, gradually exacerbated, and he developed anorexia and weight loss.

On the physical examination, respiratory distress, absent sound on auscultation, and dullness on percussion of the right lung were detected. The CXR and chest spiral computed tomography (CT) scan showed a large mass in

the right lung, right lung collapse, and mediastinal metastasis (Figure 1 B, C). The abdominal ultrasound and CT scan were normal.

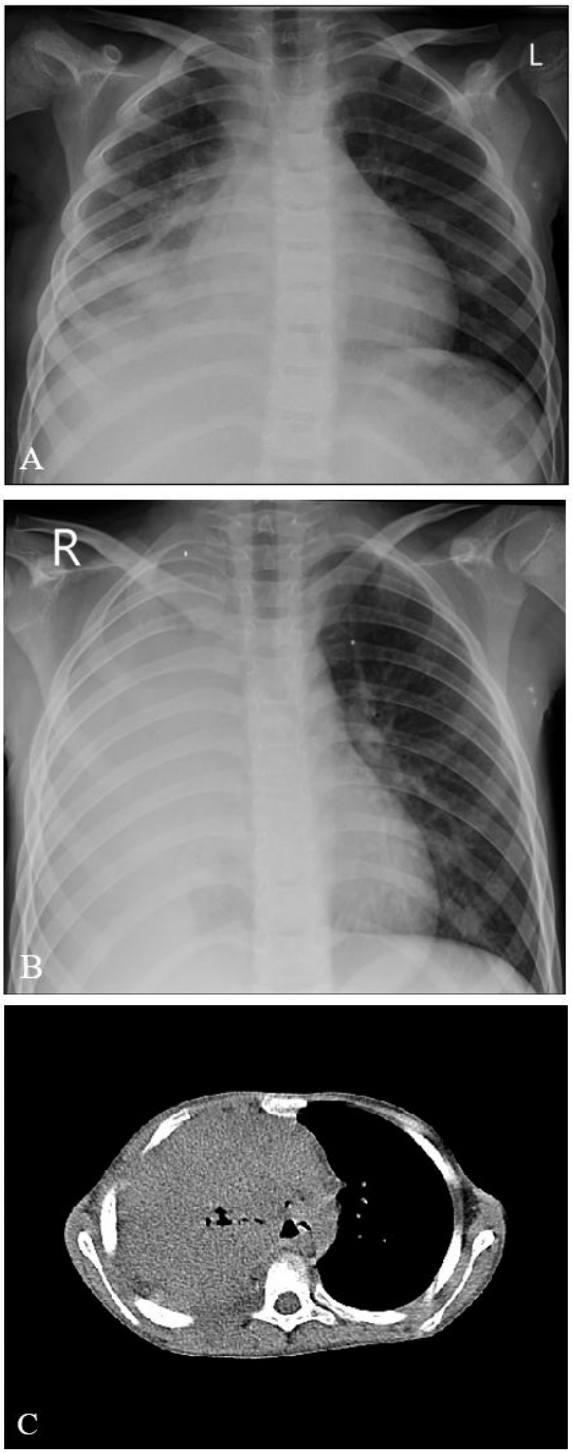

Figure 1. A) First chest X-ray of the patient at the first hospitalization showing opacity in the right lung; B and C) CXR and chest computed tomography (CT) scan showing the progression of the lung mass following discontinuation of steroids at 8.5 years old.

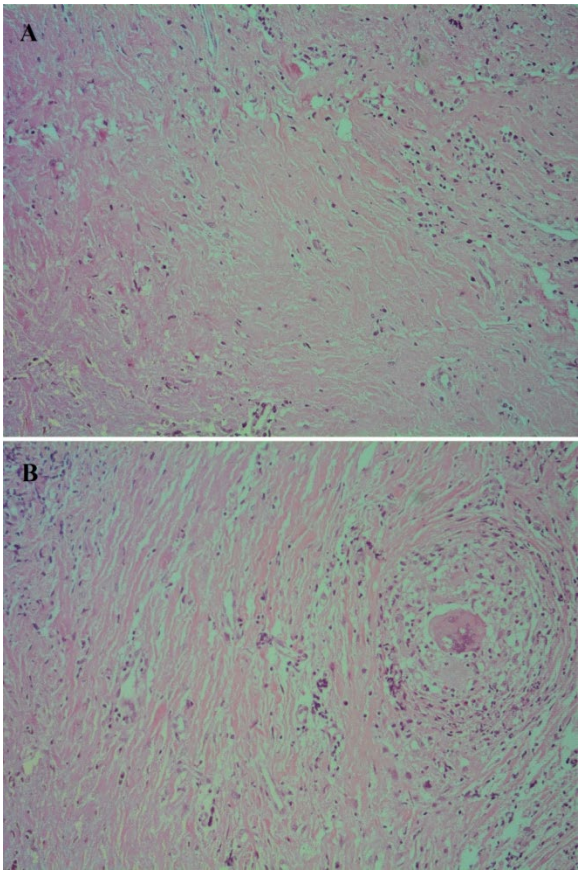

Figure 2. A) Fibrotic stroma with scattered inflammatory cells including plasma cells (H&E stain x10); B) Small non-necrotizing granuloma associated with marked peripheral fibrosis (H&E stain x10)

In laboratory evaluation, the complete blood count, leukocyte differentiation, lactate dehydrogenase, and liver function tests were normal; however, inflammatory markers (erythrocyte sedimentation rate (ESR): 112, C-reactive protein (CRP):108) were high.

In immunologic workup, low T $CD3^+$, low T $CD4^+$, low T $CD8^+$, low B $CD19^+$, low T $CD20^+$, and normal NK cells were detected. In addition, serum immunoglobulin levels included IgG: 2530 mg/dL, IgM: 178 mg/dL, IgA: 151 mg/dL, IgG1: 1885 mg/dL, IgG2: 561 mg/dL, IgG3: 32 mg/dL, and IgG4: 311 mg/dL (normal range: 1.9-93) (Table 1). The nitro blue tetrazolium (NBT) test was zero in two consecutive evaluations. In virtue of the high IgG4 level, the immunostaining of the lung specimen was performed which was inconclusive for $IgG4^+$ cells.

Table 1. Laboratory investigations in the proband

Laboratory parameters	Patient	Reference value
WBC × 10^3 (cell/uL)	15.2	6000-17000
ALC, cells /µL	**608**	3000-9500
ANC, cells /µL	**13680**	1500-8500
RBC (×10^6/ul)	3.85	4.0-5.2
Hb (gr/dL)	10.4	11.5-15.5
Plt (×10^3/ul)	249	150-450
CD3+ T cells, %, cell/µL	77.4%, **527**	1200-2600
CD4+ T cells, %, cell/µL	38.6%, **263**	650-1500
CD8+ T cells, %, cell/µL	34.0%, **232**	370-1100
$CD19^+$ B cells, %, cell/µL	2.0%, **14**	270-860
$CD20^+$ B cells, %, cell/µL	1.0%, **7**	270-860
$CD16^+$ NK cells, %	11.6%	5-19
$CD56^+$ NK cells, %	14.3%	3-15
IgG (mg/dL)	2530	>700
IgM (mg/dL)	178	>80
IgA (mg/dL)	151	>100
IgE (mg/dL)	**>400**	Up to 68
IgG1 (mg/dL)	**1885**	255-918
IgG2 (mg/dL)	**561**	44-375
IgG3 (mg/dL)	32	15-85
IgG4 (mg/dL)	**311**	1.9-93
NBT	**0**	>90
Anti-D Ab (IU/mL)	0.2	>0.01
Anti-T Ab (IU/mL)	0.14	>0.1
PT (sec)	14	9.6-12.2
INR	1.3	0.8-1.15
PTT (sec)	30	Up to 48
BUN (mg/dL)	6.8	7-17
Creatinine (mg/dL)	0.53	0.4-1
Na (meq/L)	133	135-148
K (meq/L)	4.4	5.3-4.1
P (mg/dL)	3.3	3-7
Ca (mg/dL)	8.1	8.6-10.3
ALK-P (U/L)	305	180-1200
AST (U/L)	40	<37
ALT (U/L)	38	Up to 41
Uric acid (mg/dL)	2.5	3-6.4
Mg (mg/dL)	2.2	1.5-2.3
LDH (U/L)	445	290-140
Bilirubin T (mg/dL)	1.5	0.1-1.2
Bilirubin D (mg/dL)	0.5	<0.3
CRP (mg/dL)	108	Up to 6
ESR (mm/h)	112	0-10

WBC; white blood cell, ALC; absolute lymphocyte count, ANC; absolute neutrophil count, RBC; red blood cell, Hb; hemoglobin, Plt; platelet, Ig; immunoglobulin, NBT; nitroblue tetrazolium, Anti-D; anti-diphtheria, Anti-T; anti-tetanus, NK; natural killer, PT; prothrombin time, PTT; partial thromboplastin time, INR; international normalized ratio, BUN; blood urea nitrogen, Na; Sodium, K; Potassium, P; Phosphorus, Ca; Calcium, ALK-P; alkaline phosphatase, AST; aspartate amino transferase, ALT; alanine aminotransferase, Mg; magnesium, LDH; lactate dehydrogenase, T; total, D; direct, CRP; C-reactive protein, ESR; estimated sedimentation rate

He was eventually diagnosed with concurrent CGD and IgG4RD, but progressed to respiratory failure and died despite the reinstitution of steroid therapy. Later, the other available lung specimen was evaluated postmortem by two other pathologists which showed a few $CD138^+$ cells. Unfortunately, no other tissue samples from other parts of the mass were restored for histopathologic and immunostaining purposes.

DISCUSSION

In this study, we presented the first report of pediatric IgG4RD and chronic granulomatous disease (CGD). The patient presented with progressive dyspnea, mild cough, and chest pain, and was found to have a tumor-like mass in the right lung, obstructing the airways. Following immunologic evaluation, he was diagnosed with CGD and high serum levels of IgG4.

Based on the *2020 Revised Comprehensive Diagnostic (RCD) criteria for IgG4-RD* (13), the patient has clinical and radiological features (lung mass) along with consistent serological findings (serum IgG4 levels greater than 135 mg/dL). Although in IgG4RD specific pathologic findings such as typical tissue fibrosis (particularly storiform fibrosis) or obliterative phlebitis are expected, the patient only showed extensive tissue fibrosis and inflammatory cell infiltrates. Furthermore, immunostaining of the lung mass biopsy represented a few $CD138^+$ cells. However, as stated in the above-mentioned IgG4RD criteria, the numbers of IgG4-positive cells are usually more frequent in resected organs and partially enucleated tissue, while tissue samples achieved by needle biopsy or endoscopic biopsy (as in the proband) may show lower cell numbers. Finally, the initial response to corticosteroids provides another clue for a possible IgG4RD in this case.

In recent years, some studies reported patients with both IgG4-RD and variable types of inborn errors of immunity (Table 2). In 2013, Langan et al. reported a 65-year-old female who was previously diagnosed with autoimmune lymphoproliferative syndrome (ALPS) with

FAS mutation (c. 1074delT, p. L278fs*). She had diffused pancreatic lesions, salivary gland enlargement, and right eye proptosis due to the prominence of lacrimal glands. In the microscopic evaluation of lacrimal glands, dense lymphocytic infiltration and a high number of IgG4-positive plasma cells were observed. The pancreatic lesion was eventually diagnosed as autoimmune pancreatitis and improved by steroid therapy (14).

Table 2. The overlap between IEIs and IgG4RD

Age, Sex	*IEI Type*	*IgG4RD Evidence*	*Clinical Manifestations*	*Organ of IgG4+ cell infiltration*	*Treatment*	*Outcome*	*Reference, Country*
8.5 years, Male	Chronic granulomatous disease (CGD)	High serum IgG4 (311 mg/dL), Extensive fibrosis and infiltration of mixed inflammatory cells	Dyspnea, Lung mass	Lung	Steroids	Deceased	This present report, 2023, Iran
65 years, Female	Autoimmune lymphoproliferative syndrome	Dense lymphocytic infiltrate, IgG4+ plasma cell infiltration	Enlarged salivary gland, Proptosis, Pancreatic lesions	Lacrimal gland, Pancreas	Steroids	Alive	Langan et al, 2013, USA (14)
26 years, Male	Autoimmune lymphoproliferative syndrome	High serum IgG4: 6500 mg/dL, IgG4+ plasma cell infiltration, High CD20−CD38++CD27+ plasmablasts	Organomegaly, Multiple masses in the renal cortex, Acute pancreatitis	Pancreas, Lymph node	Rapamycin, Steroids	Alive	Van de Ven et al, 2017, Germany (15)
43 years, Male	Idiopathic CD4 Lymphocytopenia	Hypocomplementemia, Increased polyclonal IgG and IgG4 subclass, increased kidney volume	Organomegaly, Pancreatic mass, Jaundice, Enlarged salivary gland, Interstitial nephritis, EBV and CMV infection, Interstitial pneumonia, Lung nodules	Kidney	Steroids	Alive	Rapisarda et al, 2015, Italy (16)
7 years, Male	Adaptive immune abnormality and EBV infection	High CD138+ plasma cells, IgG4+ plasma cell infiltration, Storiform fibrosis, Obliterative vascular lesions	Chest pain, Fever, Lymphadenopathy, Lung mass	Lung	Antibiotics, Surgical removal of mass	Alive	Szczawinska-Poplonyk et al, 2016, Poland (17)
15 months, Male	Interleukin-1 receptor-associated kinase-4 (IRAK4) deficiency	High serum IgG4 (2050 mg/dL), Lymphoplasmacytic infiltrate, significant fibrosis and focal obliterative phlebitis in histology, >100 $IgG4^+$ cells/HPF and elevated $IgG4^+/IgG^+$ plasma cell ratio in IHC	Painless unilateral eye proptosis and upper lid erythema, oral candidiasis, Staphylococcus aureus bacteremia, Klebsiella pneumoniae urosepsis, abscess	Eye	Steroids, Antibiotics, Azathioprine, Mycophenolate	Alive	Tong et al, 2021, Australia (18)
2 years, Male	Immune dysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX) syndrome	High serum IgG4 (353 mg/dL), IgG+/IgG4+ ratio of 50% in BMB, >10 IgG4+ cells/HPF and IgG+/IgG4+ ratio of 100% in kidney IHC	Bone marrow failure, Kidney failure with tubular acidosis, alopecia, candidiasis, hypoparathyroidism, maculopathy	Kidney	Steroids, HSCT, Kidney transplant	Alive	Gentile et al, 2022, Italy (19)

IEI: inborn error of immunity, BMB: bone marrow biopsy, IHC: immunohistochemistry, Ig: immunoglobulin, HSCT: hematopoietic stem cell transplantation, EBV: Epstein-Barr virus, CMV: Cytomegalovirus

Another ALPS patient with associated IgG4RD was recently described by Van de Ven et al. (15). A 26-year-old male presented with lymphadenopathy, splenomegaly, and multiple renal masses. Renal biopsy exhibited monomorphic infiltration of T $CD3^+$ lymphocytes and tubular damage. In immunologic evaluation, hypergammaglobulinemia, high serum cobalamin, interleukin (IL) -2 receptor, IL-10, and Fas ligand were identified and the genetic study confirmed the diagnosis of ALPS. He later developed acute pancreatitis and became resistant to rapamycin. The pancreatic biopsy showed lobular fibrosis and infiltrates containing eosinophils, T $CD4^+$ lymphocytes, and plasma cells (mainly IgG4 positive) and the diagnosis of IgG4RD was established. To clarify the association between IgG4RD and ALPS, they also measured IgG4 in 18 ALPS-FAS patients and found elevated IgG4 in four patients, although at lower levels than the index patient.

The underlying immune dysregulation in ALPS, including reduced tumor necrosis factor-alpha (TNF-α) expression and apoptosis of immune cells, and altered T helper 2 and T regulatory profile may explain the clinical association with IgG4RD (14). In addition, *Fas* mutation itself may contribute to the development of autoantibody-producing plasmablasts and a specific population of T cells ($CD4^+$granzyme A^+), mediating fibrosis (15). Although most of the patients with ALPS represent high levels of IgG (78.5%) (20), in those with organ lymphocytic infiltration and refractoriness to treatment, it would be reasonable to look for high levels of IgG4 and possibly IgG4RD.

In 2015, Rapisarda et al. (16) reported a 43-year-old male initially presented with cholestatic jaundice, pancreatic mass, and hepatomegaly. Later, he developed atypical interstitial pneumonitis, pulmonary nodules, lymphadenopathy, and splenomegaly with associated severe lymphopenia (including reduced $CD4^+$ T cell level), hypergammaglobulinemia, and increased inflammatory markers. The symptoms improved with the administration of glucocorticoids but recurred three years later. He also suffered from tubulointerstitial nephritis, decreased renal function, and hypocomplementemia. He was finally diagnosed with idiopathic CD4 lymphocytopenia and IgG4RD and treated with prednisolone.

The first report of IgG4RD in a pediatric patient with immunodeficiency was presented by Szczawinska-Poplonyk et al. (17). The patient was a 7-year-old male with a history of allergic rhinitis and bronchitis who presented with fever, respiratory distress, and lymphadenopathy. Pneumonia was suspected but did not improve with intravenous antibiotics. A consolidated mass was detected through the chest CT scan and surgically removed. The histopathology showed infiltration of lymphoplasmacytes, fibrosis, and vasculitis. Laboratory workup revealed increased $CD8^+$ T cells, decreased $CD4^+$ T cells, decreased memory B cells, EBV viremia, and no autoantibodies. He was diagnosed with IgG4RD and improved without complication.

In 2021, Tong et al. (18) described another pediatric patient with interleukin-1 receptor-associated kinase-4 (*IRAK4)* deficiency and concomitant IgG4RD. The patient was a 15-month-old male who presented with painless unilateral eye proptosis and upper lid erythema and a history of oral candidiasis, *Staphylococcus aureus* bacteremia, *Klebsiella pneumonia* urosepsis, and an abscess on the right hand. He was found to have high serum IgG4 and evidence of IgG4RD in the histopathologic examination. In MRI, dural enhancement was observed and lacrimal glands were spared. Treatment with prednisolone, azathioprine, and trimethoprim-sulfamethoxazole (and later mycophenolate) was commenced and improved the orbital disease. He subsequently developed intestinal pseudo-obstruction, Pseudomonas meningoencephalitis, and CMV viremia and was found to have a homozygous mutation in *IRAK4*.

Similarly, in a recent case study by Gentile et al (19), the diagnosis of IgG4RD preceded the diagnosis of IEI. The patient was a 2-year-old male who was admitted due to trilinear cytopenia and during hospitalization developed kidney failure with tubular acidosis. A kidney biopsy revealed tubulointerstitial lymphoplasmacytic infiltrates,

irregular thickening of the glomerular basement membrane, glomerular and tubular IgG deposits, and glomerular C3 deposits. IHC evaluation of kidney biopsy showed >10 $IgG4^+$ cells/HPF and $IgG^+/IgG4^+$ ratio of 100%, which along with high serum levels of IgG suggested an underlying IgG4RD. Later, he was complicated with alopecia, candidiasis with hepatic involvement, and hypoparathyroidism. The genetic study demonstrated a hemizygous mutation in FOXP3 (c.1087A>G, p.I363V) confirming the diagnosis of immune dysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX) syndrome.

Further studies on patients with inborn errors of immunity with clinical presentations of IgG4RD are required to elucidate possible common pathologic pathways between these two immune-mediated disorders. Along with searching for possible susceptibility variants that drive class switching to IgG4 and clonal expansion of $CD4^+$ cytotoxic T cells (21), the role of epigenetic factors such as exposure to variable organisms in the context of immunodeficiency should not be neglected..

CONCLUSION

To recapitulate, the overlap between inborn errors of immunity (IEIs) and IgG4RD is not common and this case represents the first CGD patient with associated IgG4RD. In CGD, pulmonary mass due to IgG4RD may be misdiagnosed as pulmonary granuloma, requiring further studies to elucidate the etiology. As IgG4RD is recurrent in nature, after the diagnosis is established, close monitoring of patients would prevent irreversible organ damage.

Ethics approval and consent to participate

Informed consent was obtained from the patient and parents of the patient before being included in the study.

Competing interests

The authors declare that they have no conflict of interest.

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REFERENCES

1. Casanova JL, Abel L. Lethal Infectious Diseases as Inborn Errors of Immunity: Toward a Synthesis of the Germ and Genetic Theories. ***Annu Rev Pathol*** 2021;16:23-50.
2. Yu HH, Yang YH, Chiang BL. Chronic Granulomatous Disease: a Comprehensive Review. ***Clin Rev Allergy Immunol*** 2021;61(2):101-13.
3. Kulkarni M, Desai M, Gupta M, Dalvi A, Taur P, Terrance A, et al. Clinical, Immunological, and Molecular Findings of Patients with $p47^{phox}$ Defect Chronic Granulomatous Disease (CGD) in Indian Families. ***J Clin Immunol*** 2016;36(8):774-84.
4. Henrickson SE, Jongco AM, Thomsen KF, Garabedian EK, Thomsen IP. Noninfectious Manifestations and Complications of Chronic Granulomatous Disease. ***J Pediatric Infect Dis Soc*** 2018;7(suppl_1):S18-S24.
5. Campos LC, Di Colo G, Dattani V, Braggins H, Kumararatne D, Williams AP, et al. Long-term outcomes for adults with chronic granulomatous disease in the United Kingdom. ***J Allergy Clin Immunol*** 2021;147(3):1104-7.
6. Yao Q, Zhou QH, Shen QL, Qiao ZW, Wang XC, Hu XH. Imaging findings of pulmonary manifestations of chronic granulomatous disease in a large single center from Shanghai, China (1999-2018). ***Sci Rep*** 2020;10(1):19349.
7. Martire B, Rondelli R, Soresina A, Pignata C, Broccoletti T, Finocchi A, et al. Clinical features, long-term follow-up and outcome of a large cohort of patients with Chronic Granulomatous Disease: an Italian multicenter study. ***Clin Immunol*** 2008;126(2):155-64.
8. Mahdaviani SA, Mohajerani SA, Rezaei N, Casanova JL, Mansouri SD, Velayati AA. Pulmonary manifestations of chronic granulomatous disease. ***Expert Rev Clin Immunol*** 2013;9(2):153-60.
9. Karim F, Loeffen J, Bramer W, Westenberg L, Verdijk R, van Hagen M, et al. IgG4-related disease: a systematic review of this unrecognized disease in pediatrics. ***Pediatr Rheumatol Online J*** 2016;14(1):18.
10. Lu H, Teng F, Zhang P, Fei Y, Peng L, Zhou J, et al. Differences in clinical characteristics of IgG4-related disease across age groups: a prospective study of 737 patients. ***Rheumatology (Oxford)*** 2021;60(6):2635-46.

11. Grewal K, Cohen P, Kwon JS, Kaufman DA. IgG4-related disease presenting as a lung mass and weight loss: Case report and review of the literature. ***Respir Med Case Rep*** 2015;17:27-9.
12. Pandita A, Wong J. IgG4-related disease in lung: a diagnostic challenge. ***Pathology*** 2020;52(3):390-2.
13. Umehara H, Okazaki K, Kawa S, Takahashi H, Goto H, Matsui S, et al. The 2020 revised comprehensive diagnostic (RCD) criteria for IgG4-RD. ***Mod Rheumatol*** 2021;31(3):529-33.
14. Langan RC, Gill F, Raiji MT, Mullinax JE, Pittaluga S, Pandalai P, et al. Autoimmune pancreatitis in the autoimmune lymphoproliferative syndrome (ALPS): a sheep in wolves' clothing? Pancreas. 2013 Mar;42(2):363-6.
15. van de Ven AAJM, Seidl M, Drendel V, Schmitt-Graeff A, Voll RE, Rensing-Ehl A, et al. IgG4-related disease in autoimmune lymphoproliferative syndrome. ***Clin Immunol*** 2017;180:97-9.
16. Rapisarda F, Zanoli L, Portale G, Scuto S, Castellino P. A Case Report of an Atypical Presentation of IgG4-Related Disease and Idiopathic CD4 Lymphocytopenia. Case Rep Med. 2015;2015:512370.
17. Szczawinska-Poplonyk A, Wojsyk-Banaszak I, Jonczyk-Potoczna K, Breborowicz A. Pulmonary manifestation of immunoglobulin G4-related disease in a 7-year-old immunodeficient boy with Epstein-Barr virus infection: a case report. ***Ital J Pediatr*** 2016;42(1):58.
18. Tong JY, Leahy KE, Wong M, Krivanek M, Tumuluri K. IgG4-related disease of the orbit in an infant. ***J AAPOS*** 2021;25(4):255-7.
19. Gentile M, Miano M, Terranova P, Giardino S, Faraci M, Pierri F, et al. Case Report: Atypical Manifestations Associated With FOXP3 Mutations. The "Fil Rouge" of Treg Between IPEX Features and Other Clinical Entities? ***Front Immunol*** 2022;13:854749.
20. Hafezi N, Zaki-Dizaji M, Nirouei M, Asadi G, Sharifinejad N, Jamee M, et al. Clinical, immunological, and genetic features in 780 patients with autoimmune lymphoproliferative syndrome (ALPS) and ALPS-like diseases: A systematic review. ***Pediatr Allergy Immunol*** 2021;32(7):1519-32.
21. Mattoo H, Stone JH, Pillai S. Clonally expanded cytotoxic $CD4^+$ T cells and the pathogenesis of IgG4-related disease. ***Autoimmunity*** 2017;50(1):19-24.