SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2020; 37 (2); 225-230 DOI: 10.36141/svdld.v37i2.9098

Non-tuberculous, adenosine deaminase-positive lymphocytic pleural effusion: Consider immunoglobulin G4-related disease

Ori Wand[1,2,3], Benjamin D Fox2,[4], Osnat Shtraichman[1,2], Osnat Moreh-Rahav[2,5], Mordechai R Kramer[1,2]

[1] Pulmonary Institute, Rabin Medical Center, Beilinson Campus, Petach Tiqwa, Israel; [2] Sackler Faculty of Medicine, Tel Aviv University, Israel; [3] Pulmonary Division, Meir Medical Center, Kfar-Sava, Israel; [4] Pulmonary Institute, Assaf Harofeh Medical Center, Tzrifin, Israel; [5] Radiology Department, Edith Wolfson Medical Center, Holon, Israel.

Abstract. *Objective:* Immunoglobulin G4-related disease (IgG4-RD) is a recently described systemic disorder. Pleural effusion is considered an uncommon manifestation of the disease. We describe a case series of patients with IgG4-RD and clinically significant pleural effusions. *Methods:* A retrospective analysis of patients with histologically proven IgG4-RD treated for pleural effusion in our clinic. *Results:* We identified 4 male patients with pleural effusion caused by IgG4-RD. The effusions were lymphocytic exudates, with especially high protein concentrations. All patients had hyperglobulinemia, elevated serum immunoglobulin G (IgG) levels and elevated levels subclasses IgG1 and IgG4. In two patients, levels of adenosine deaminase (ADA) were measured in the effusion and were elevated (309 and 108 IU/L). Tuberculosis was excluded in both cases by pleural biopsy. Involvement of other organs by IgG4-RD was the rule, especially thoracic lymphadenopathy which was prominent in all patients. In all cases, effusion responded to corticosteroids therapy. One patient developed radiological findings compatible with rounded atelectasis during remission. *Conclusions:* IgG4-RD may cause an ADA-positive, lymphocytic exudate with a high protein concentration, characteristics resembling tuberculous effusion. Thoracic lymphadenopathy, hyperglobulinemia, and an increased total IgG, IgG1, IgG4 may suggest the diagnosis. Not previously described, IgG4-RD pleural inflammation may result in rounded atelectasis. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (2): 225-230)*

Key words: Immunoglobulin G4-related disease, IgG4-related disease, tuberculosis, ADA, pleural effusion, adenosine deaminase

Introduction

Immunoglobulin G4 related disease (IgG4-RD) is a systemic disorder with involvement of various organs. The condition is characterized by lymphoplasmacytic infiltration of single or multiple organs, resulting in mass lesions and/or organ dysfunction. Additional histological features include: storiform fibrosis and obliterative phlebitis, and abundance of IgG4-positive plasma cells in involved organs, often with elevated IgG4 serum levels [1-2]. Pulmonary manifestations of IgG4-RD may include involvement of the lung parenchyma, airways, vasculature, pleural spaces, and thoracic lymph nodes [1]. Pleural effusion is considered an uncommon manifestation of IgG4-RD, mainly mentioned in case reports.

Methods

We conducted a retrospective analysis of patients with a pleural effusion secondary to IgG4-RD who were treated in our clinic from January 2009 to December 2017. We assessed patients' clinical, radiographic, laboratory and pathological data, treatment and outcome. We included only cases with

Received: 15 December 2019
Accepted after revision: 20 May 2020
Correspondence: Dr. Ori Wand
Pulmonary Division, Meir Medical Center, 59 Tsernichowski St., Kfar-Sava, Israel, 4428164.
Tel: 972-97471556
ORCID ID: 0000-0002-7702-2967
Ori.wand@clalit.org.il

an established diagnosis of IgG4-RD (based on accepted criteria, including both the Boston pathologic criteria and the Japanese comprehensive and organ-specific criteria [2-3]), who had pleural effusions requiring evaluation or management with pleurocentesis. The study was approved by the Rabin Medical Center Institution Review Board (application No. RMC-0869-17) and in accordance with the Declaration of Helsinki and with Good Clinical Practice guidelines. Due to the retrospective nature of the study, a written informed consent was not required.

Results

We identified four patients with pleural effusion caused by IgG4-RD. All patients were males, mean age 74-years at time of diagnosis. One of the patients was a smoker with a history of chronic obstructive pulmonary disease (COPD). None of the patients had a history of other respiratory diseases, relevant occupational or environmental exposure, and none had known exposure to tuberculosis (TB). Human Immunodeficiency Virus (HIV) status was negative for all cases. All cases presented with dyspnea. Additional clinical and laboratory data are detailed in Table 1.

All patients had polycloncal hyperglobulinemia, with elevated serum concentrations of immunoglobulin G (IgG) and subclasses IgG4 and IgG1.

Radiographically, pleural effusions were bilateral in 3 cases and right-sided only in one case. Prominent enlargement of mediastinal and hilar lymph nodes was demonstrated in all patients. Two patients had additional parenchymal involvement in the form of diffuse ground glass opacities (GGO) consolidations.

Diagnosis of IgG4-RD was based on accepted criteria, including: organ involvement, elevated serum levels of IgG4, pathological features supporting the diagnosis and exclusion of other alternative diagnoses [2-3]. One patient had a prior diagnosis of IgG4-RD cholangitis and liver involvement supported by a liver biopsy. In the 3 other cases, pleural effusions were part of the initial presentation of IgG4-RD. Diagnosis of IgG4-RD was supported by a surgical pleural biopsy in case 2, by an excisional biopsy of a peripheral lymph node in case 4, and in cases 2 and 3 by a transbronchial biopsy. In case no. 3, transbronchial biopsies demonstrated a lymphoplasmacytic infiltrate with areas suggesting organizing pneumonia pattern, and abundant IgG4 positive cells. Thus, in all cases a diagnosis of definite or probable IgG4-Related respiratory disease was established [2-3].

Pleural effusions were exudates in all cases, with especially high protein concentrations and elevated concentrations of lactate dehydrogenase (LDH). There was a striking lymphocytic predominance in the cell counts, with no decrease in glucose and pH levels. In all cases bacterial and mycobacterial cultures were negative, and cytological evaluation was negative for malignancy.

Levels of adenosine deaminase (ADA) were measured in two patients and were elevated at 309 and 108 IU/L, respectively. In both cases TB was excluded by negative tissue cultures and histology of pleural biopsies specimens. In case no. 2, histological and immunohistochemical evaluation of the pleura fulfilled criteria for the diagnosis of definite IgG4-RD, specifically, a lymphoplasmacytic infiltrate with increased number of IgG and IgG4 positive cells was demonstrated in pleural biopsy specimens as well as in transbronchial biopsy specimens of the lung. In case no. 4 pleural biopsy demonstrated signs of non-specific chronic lymphocytic inflammation and a diagnosis of probable IgG4-RD was established by an excisional biopsy of an inguinal lymph node [2-3]. In both cases, Acid Fast stains and tissue cultures of the pleura were negative, and no granulomas were identified.

All four patients were treated with oral prednisone 0.5-1mg/kg daily as initial dose. All had good responses to steroid therapy with clinical improvement, as well as significant reduction in the size of pleural effusion and volume of lymph nodes, occurring within 4 weeks of therapy, and prednisone dosing was therefore gradually tapered down over several months. Patients no. 1 and 2 were able to stop prednisone completely after 9 and 7 months respectively. Patient 3 required ongoing immunosuppression, and azathioprine was added after 6 months of prednisone therapy, ultimately allowing complete steroid withdrawal. In case no. 4, steroid dose was quickly tapered down due to uncontrolled diabetes. His initial elevated level of ADA (108 IU/L) in the effusion was reduced (32 IU/L) with repeated therapeutic pleurocentesis. He was then treated with rituximab as a steroid sparing agent, with two doses of 1g given 14-days apart, resulting in long-term remission of his illness. However, follow-up computed tomography

Table 1. Data of patients with pleural effusion due to IgG4-RD

Case No.	**1**	**2**	**3**	**4**
Age	75	68	84	68
Sex	M	M	M	M
Serum studies (normal range)				
Globulins g/dL (2.0-3.5)	5.2	4	3.9	5.2
IgG mg/dL (700-1600)	4520	2491	2620	3030
IgG1 mg/dL (405-1011)	1967	NA	2010	1851
IgG4 mg/dL (3-201)	1170	NA	1420	297
Effusion studies (normal range in serum)				
Side	right	bilateral	bilateral	bilateral
White blood cells	NA	2900	2385	1326
Lymphocytes%	NA	96	88	85
LDH (effusion/serum) U/L (230-460) (ratio)	770/359 (2.15)	908/866 (1.05)	382/287 (1.33)	272/428 (0.64)
Protein (effusion/serum) g/dL (6.0-8.2) (ratio)	5.6/9.0 (0.62)	7.0/7.1 (0.99)	7.4/7 (1.06)	6.9/8.7 (0.79)
Glucose (effusion/serum) mg/dL (70-100) (ratio)	115/120 (0.96)	273/294 (0.93)	69/98 (0.70)	107/121 (0.88)
pH	7.30	7.39	7.34	7.41
ADA IU/L	NA	309	NA	108
Pleural biopsy				
Performed?	-	+	-	+
Diagnostic of IgG4-RD?	NA	+	NA	-
Level of diagnostic certainty for IgG4-RD	Established	Established	Established	Probable (Highly)
Histopathological confirmation for IgG4-RD derived from	Liver biopsy	Pleural and transbronchial biopsy	Transbronchial biopsy	Peripheral lymph node
Additional organ involvement by IgG4-RD	Liver and biliary, thoracic LNE	Lung parenchymal, thoracic LNE	Lung parenchymal, thoracic LNE	Generalized LNE
Response to steroid treatment	+	+	+	+

LNE – lymph nodes enlargement

6 months later demonstrated the development of rounded atelectasis in the right lung (Figure 1).

Discussion

Indeed, intrathoracic involvement in IgG4-RD is common, while pleural effusions are an unusual, yet a clinically significant manifestation [4-8]. In a prospective study by *Fei et al.*, intrathoracic lesions were identified in 87/248 cases with IgG4-RD, yet with pleural effusions in only 4 cases [8]. In a UK study by *Corcoran et al.*, 22/53 (42%) patients were categorized according to thoracic cross-sectional imaging studies as having thoracic involvement by IgG4-RD, yet only three patients had pleural effusions [9].

We have reviewed the literature for studies of large cohorts of patients with IgG4-RD (n > 20) and which report pulmonary or pleural involvement. We've identified 24 such studies from different countries, including a total of 1796 patients with IgG4-RD [8-9, 19-40]. The prevalence of pulmonary involvement in those series varied widely, from 3.6% to 59%, and was defendant on the study's design. Thus, the percentage of patients with pulmonary involvement was higher in studies in which CT of the chest was routine. The presence of pleural effusions was not

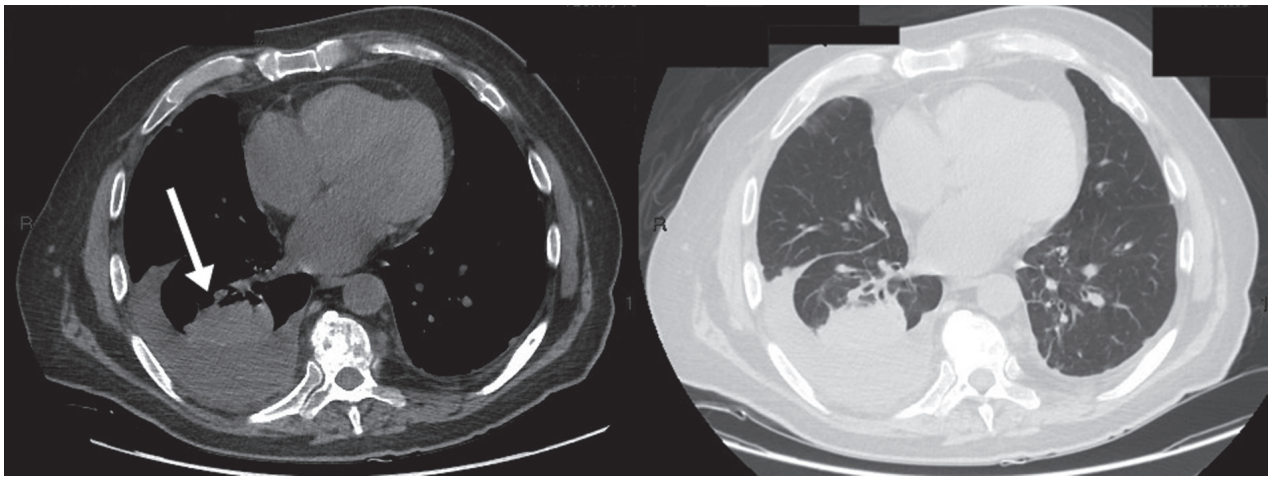

Fig. 1. Rounded atelectasis in a patient with IgG4-RD
CT of the chest from patient no. 4, demonstrating thickened pleura and a small effusion with signs of rounded atelectasis on the right (arrow).

addressed at all in six of the reviewed studies. From the remaining 18 studies which comprise 1228 patients, the prevalence of pleural effusions reached up to 5.7%, but was 0% in 14/18 studies. Thus, in the majority of large series of patients with IgG4-RD, no cases of pleural effusion were reported, while in a few studies they were very uncommon

Patients with IgG4-RD and pleural effusions have mostly been described in case reports. In addition to reporting two new cases, a literature review from 2016 also identified 13 previous case reports. In their review, 72% of patients were male with a mean age of 65, 55% had bilateral effusions and all cases had elevated serum levels of IgG4. In the majority (83%), additional organs involvement was described, mostly lungs, pericardium, and mediastinum. The authors suggest that serosal involvement by IgG4-RD, including pleural effusion, might be more common than previously considered [10]. This concurs to our experience, thus we agree that pleural effusions secondary to IgG4-RD are probably under-recognized and subsequently under-reported.

ADA, an enzyme involved in purine metabolism, catalyzes the deamination of adenosine to inosine and of deoxyadenosine to deoxyinosine. The enzyme is involved in the proliferation and differentiation of lymphocytes, specifically the T-lymphocytes. T-cells activation in the presence of live intracellular pathogens includes the release ADA, thus considered a marker of cell-mediated immune response [11]. Nonetheless, interpretation of ADA measurements in the evaluation of lymphocytic pleural effusions is complex. In endemic areas, positive results (> 35-40 IU/L) are highly sensitive and specific for tuberculosis (TB) and anti-tuberculous therapy is usually indicated [11]. Even in populations with a low incidence of TB, a positive ADA in a lymphocytic effusion, although very uncommon, still strongly suggests TB, while a negative result can exclude tuberculous pleural effusion [12]. In a large prospective study among 410 patients, pleural fluid ADA was elevated in only 7 (1.7%) patients with nontuberculous lymphocytic effusions [13]. Thus, an undiagnosed ADA-positive lymphocytic effusion in a low incidence population should prompt further evaluation including pleural biopsy. There are a few case reports of patients with IgG4-RD and an elevated pleural fluid ADA. A recent report from 2018 describes such a case and reviews 4 additional case reports [14].

In TB, stimulation of T cells by mycobacterial antigens results in increased ADA levels. However, the mechanisms associated with elevations of ADA levels in the pleural fluid of patients with IgG4-RD are unknown. In IgG4-RD, Th2-cell responses are predominantly activated at affected sites. While in contrast, in classic autoimmune conditions, the function of regulatory T-cells (Treg) cells is impaired. The mechanisms involved in IgG4-RD pathophysiology

are supported by large infiltrates of $CD4^+CD25^+$ Treg cells at affected sites [15]. Interestingly, similar to observations in TB patients [16], suggesting a possible common pathway of immune response inducing high ADA levels.

To the best of our knowledge, we describe the first case of rounded atelectasis solely attributed to IgG4-RD. In one other report, the patient had significant long-term occupational exposure to asbestos, resulting in stable round atelectasis for 8 years before the first symptoms of IgG4-RD emerged [17].

Many of the findings from our single center case series correlate with previous reports of cases with IgG4-RD pleural effusion. Most patients with IgG4-RD in general are elderly men, frequent clinical findings include elevated serum levels of IgG and IgG4 (in our series also of IgG1), and additional organ involvement of the disease, most commonly thoracic lymphadenopathy [18, 41]. Thus, our report adds significant information to the little data available regarding pleural effusions in IgG4-RD.

In summary, although uncommon, pleural effusion can be a manifestation of IgG4-RD, and even part of the initial presentation of the disease. IgG4-RD may cause an ADA-positive lymphocytic exudate, resembling tuberculous effusion. Clinicians should consider IgG4-RD in the differential diagnosis of an ADA-positive pleural effusion, which are very uncommon in areas with a low incidence of TB. In the absence of extra-thoracic involvement, clinical signs suggesting such diagnosis are mediastinal and hilar lymphadenopathy, polyclonal hyperglobulinemia, and elevated levels of IgG, IgG1 and IgG4. A pleural biopsy can aid in confirming the diagnosis. Pleural inflammation by IgG4-RD may also result in the development of rounded atelectasis.

Acknowledgments

The authors wish to thank Dalia Orkin from Medic-Write for editorial assistance.

The study was self-funded by the Pulmonary Institute at the Rabin Medical Center.

The authors report no conflict of interest regarding this manuscript. The study was self-funded by the Pulmonary Institute of Rabin Medical Center.

References

1. Ryu JH and Yi ES. Immunoglobulin G4-Related Disease and the Lung. Clin Chest Med 2016; 37:569–78.
2. Deshpande V, Zen Y, Chan JKC, Yi EE, Sato Y, et a. Consensus Statement on the Pathology of IgG4-Related Disease. Modern Pathology 2012; 25:1181–1192.
3. Umehara H, Okazaki K, Nakamura T, Satoh-Nakamura T, Nakajima A, et al. Current Approach to the Diagnosis of IgG4-Related Disease – A Combination of Comprehensive Diagnostic and Organ-Specific Criteria. Mod Rheumatol 2017; 27:381–91.
4. Ryu JH and Yi ES. Pulmonary Manifestations of Immunoglobulin G4-Related Sclerosing Disease. Eur Respir J 2012; 39:180–6.
5. Brito-Zerón P, Ramos-Casals M, Bosch X, and Stone JH. The Clinical Spectrum of IgG4-Related Disease. Autoimmunity Review 2013; 13:1203–10.
6. Corcoran JP, Culver EL, Psallidas I, Hallifax RJ, Davies SJ, et al. A 63-year-old Man with a Recurrent Right-Sided Pleural Effusion. Thorax 2015; 70:504–7.
7. Ramponi S, Gnetti L, Marvisi M, Bertorelli G, and Chetti A. Lung Manifestations of IgG4-Related Disease. A Multifaceted Disorder. Sarcoidosis Vasc Diffuse Lung Dis 2018; 35:74–80.
8. Fei Y, Shi J, Lin W, Chen Y, Feng R, et al. Intrathoracic Involvements of Immunoglobulin G4-Related Sclerosing Disease. Medicine 2015; 94:e2150.
9. Corcoran JP, Culver EL, Anstey RM, Talwar A, Manganis CD, et al. Thoracic Involvement in IgG4-Related Disease in a UK-Based Patient Cohort. Respir Med 2017; 132:117–21.
10. Gonzáles-Moreno J, Losada-López I, Gállego-Lezaun C, García-Gasalla M, Bellvert CJ, and Centeno NO. Serosal Involvement in IgG4-Related Disease: Report of Two Cases and Review of the Literature. Rheumatol Int 2016; 36:1033–41.
11. Light RW. Update on tuberculous pleural effusion. Respirology 2010; 15:451–8.
12. Arnold DT, Bhatnagar R, Fairbanks LD, Zahan-Evans N, Clive AO, et al. Pleural Fluid Adenosine Deaminase (Pfada) in the Diagnosis of Tuberculous Effusions in a Low Incidence Population. PLoS ONE 2015; 10:e0113047.
13. Jiménez Castro D, Díaz Nuevo G, Pérez-Rodríguez E, and Light RW. Diagnostic Value of Adenosine Deaminase in Nontuberculous Lymphocytic Pleural Effusions. Eur Respir J 2003; 21:220–4.
14. Nagayasu A, Kubo S, Nakano K, Nakayamada S, Iwata S, et al. IgG4-Related Pleuritis with Elevated Adenosine Deaminase in Pleural Effusion: A Case Report. Intern Med 2018; 57:2251–7.
15. Stone JH, Zen Y, and Deshpande V. IgG4-Related Disease. N Engl J Med 2012; 366:539–51.
16. Parkash O, Agrawal S, and Madhan Kumar M. T Regulatory Cells: Achilles' Heel of Mycobacterium Tuberculosis Infection? Immunol Res 2015; 62:386–98.
17. Onishi Y, Nakahara Y, Hirano K, Sasaki S, Kawamura T, and Mochiduki Y. IgG4-Related Disease in Asbestos-Related Pleural Disease. Respirol Case Rep 2015; 4:22–4.
18. Stone JH, Brito-Zerón P, Bosch X, and Ramos-Casals M. Diagnostic Approach to the Complexity of IgG4-Related Disease. Mayo Clin Proc 2015; 90:927–39.
19. Masaki Y, Dong L, Kurose N, et al. Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: Analysis of 64 cases of IgG4-related disorders. Ann Rheum Dis 2009; 68: 1310–5.
20. Zen Y, Inoue D, Kitao A, et al. IGG4-related lung and pleural disease: a clinicopathologic study of 21 cases. Am J Surg Pathol 2009; 33:1886–93.
21. Fujinaga Y, Kadoya M, Kawa S, et al. Characteristic findings in images of extra-pancreatic lesions associated with autoimmune pancreatitis. Eur J Radiol 2010; 76:228–38.

22. Zen Y and Nakanuma Y. IgG4-related disease: A cross-sectional study of 114 cases. Am J Surg Pathol 2010; 34:1812–9.
23. Ebbo M, Daniel L, Pavic M, et al. IgG4-related systemic disease: features and treatment response in a French cohort. Medicine (Baltimore) 2012; 91:49–56.
24. Patel H, Khalili K, Kyoung KT, et al. IgG4 related disease: a retrospective descriptive study highlighting Canadian experiences in diagnosis and management. BMC Gastroenterol 2013; 13:168 doi: 10.1186/1471-230X-13-168.
25. Zhang J, Chen H, Ma Y, et al. Characterizing IgG4-related disease with ^{18}FDG PET/CT: A prospective cohort study. Eur J Nucl Med Mol Imaging 2014; 41:1624–34.
26. Chen H, Lin W, Wang Q, et al. IgG4-related disease in a Chinese cohort: A prospective study. Scand J Rheumatol 2014; 43:70–4.
27. Huggett MT, Culver EL, Kumar M, et al. Type 1 autoimmune pancreatitis and IgG4-related sclerosing cholangitis is associated with extrapancreatic organ failure, malignancy, and mortality in a prospective UK cohort. Am J Gastroenterol 2014; 109:1675–83.
28. Wallace ZS, Deshpande V, Mattoo H, et al. IgG4-related disease: clinical and laboratory features in one hundred twenty-five patients. Arthritis Rheumatol 2015; 67:2466–75.
29. Lin W, Lu S, Chen H, et al. Clinical characteristics of immunoglobulin G4-related disease: a prospective study of 118 Chinese patients. Rheumatology 2015; 54:1982–90.
30. Fernández-Codina A, Martínez-Valle F, Pinilla B, et al. IgG4-related disease: Results from a multicenter Spanish registry. Medicine 2015; 94: e1275. doi: 10.1097/MD.0000000000001275.
31. Inoue D, Yoshida K, Yoneda N, et al. IgG4-related disease: Dataset of 235 consecutive patients. Medicine 2015; 94: e680. doi: 10.1097/MD.0000000000000680.
32. Carruthres MN, Topazian MD, Khosroshahi A, et al. Rituximab for IgG4-related disease: a prospective, open-label trial. Ann Rheum Dis 2015; 74:1171–7.
33. Campochiaro C, Ramirez GA, Bozzolo EP, et al. IgG4-related disease in Italy: Clinical features and outcomes of a large cohort of patients. Scand J Rheumatol 2016; 45:135–45.
34. Saraya T, Ohkuma K, Fujiwara M, et al. Clinical characterization of 52 patients with immunoglobulin G4-related disease in a single tertiary center in Japan: Special reference to lung disease in thoracic high-resolution computed tomography. Respir Med 2017; 132: 62–7.
35. Masaki Y, Matsui S, Saeki T, et al. A multicenter phase II prospective clinical trial of glucocorticoid for patients with untreated IgG4-related disease. Mod Rheumatol 2017; 27:849–54.
36. Gupta N, Mathew J, Mohan H, et al. Addition of second-line steroid sparing immunosuppressant like mycophenolate mofetil improves outcome of immunoglobulin G4-related disease (IgG4-RD): A series from a tertiary care teaching hospital in South India. Rheumatol Int 2018; 38:203–9.
37. Fong W, Liew I, Tan D, et al. IgG4-related disease: Features and treatment response in a multi-ethnic cohort in Singapore. Clin Exp Rheumatol 2018; 36 Suppl 112:89–93.
38. Karim AF, Bansie RD, Rombach SM, et al. The treatment outcomes in IgG4-related disease. Neth J Med 2018; 76:275–85.
39. Fernández-Codina A, Pinilla B, Pinal-Fernández I, et al. Treatment and outcomes in patients with IgG4-related disease using the IgG4 responder index. Joint Bone Spine 2018; S1297-319X(18)30017-4. doi: 10.1016/j.jbspin.2018.01.014. [Epub ahead of print].
40. Cheng MF, Guo YL, Yen RF, et al. Clinical utility of FDG PET/CT in patients with autoimmune pancreatitis: A case control study. Sci Rep 2018; 8(1):3651. doi: 10.1038/s41598-018-21996-5.
41. Keenan JC, Miller E, Jessurun J, Allen T, and Kim HJ. IgG4-Related Disease of the Lung: A Case Series of 6 Patients and Review of the Literature. Sarcoidosis Vasc Diffuse Lung Dis 2015; 32:360–67.