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【 CASE REPORT 】

Acute Tubulointerstitial Nephritis in Rosai-Dorfman Disease Mimicking IgG4-related Disease

Satoshi Kurahashi[1], Naohiro Toda[1], Masaaki Fujita[2], Katsuya Tanigaki[1], Jun Takeoka[1], Hisako Hirashima[1], Eri Muso[1], Katsuhiro Io[3], Takaki Sakurai[4] and Toshiyuki Komiya[1]

Abstract:
Rosai-Dorfman-Destombes disease (RDD) is a non-Langerhans cell histiocytosis characterized by the accumulation of histiocytes inside the lymph nodes or extranodally. The association between RDD and IgG4-related disease (IgG4-RD) is discussed. We herein report a case of RDD manifesting as acute tubulointerstitial nephritis mimicking IgG4-RD. The first renal biopsy showed severe tubulointerstitial nephritis with infiltration of S100-positive histiocytes and IgG4-positive plasma cells; storiform fibrosis and obliterative phlebitis were not confirmed. After prednisolone therapy, IgG4-positive cells and S100-positive histiocytes were decreased, but the IgG4/IgG ratio increased despite clinical improvement. These findings indicated extranodal RDD in the kidney presenting as tubulointerstitial nephritis.

Key words: Rosai-Dorfman disease, IgG4-related disease, tubulointerstitial nephritis

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Introduction

Rosai-Dorfman-Destombes disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a rare non-Langerhans cell histiocytosis characterized by the accumulation of activated histiocytes within affected tissues. Histological confirmation of emperipolesis, i.e. the engulfment of intact leukocytes into the cytoplasm of histiocytes, is required for the diagnosis. The immunophenotype of these large RDD histiocytes is S100- and CD68-positive and CD1a-negative (1). RDD presents clinically as lymphadenopathy with or without an intermittent fever, night sweating, and weight loss. Extranodal involvement is reported in 43% of RDD cases, and kidney manifestations of RDD are reported in only 4% of extranodal cases (1, 2). Most kidney involvement cases present with renal hilar mass, whereas renal parenchymal lesions without tumor mass are rare (1).

IgG4-related disease (IgG4-RD) is a fibroinflammatory condition characterized by tumefactive lesions, a dense lymphoplasmacytic infiltrate rich in IgG4-positive cells, storiform fibrosis, and often elevated serum IgG4 concentrations. Tubulointerstitial nephritis with dominant IgG4-positive plasma cell infiltration and fibrosis is the most common histological finding in renal involvement of IgG4-RD (3). Recently, several studies have reported increased IgG4-positive plasma cell counts and elevated IgG4/IgG ratios in organs other than the kidney that are affected by RDD, such as the pancreas, lymph node, skin, and breast (4, 5).

We herein report a case of acute tubulointerstitial nephritis in Rosai-Dorfman disease with infiltration of IgG4-positive plasma cells.

Case Report

A 76-year-old man with lymphadenopathy and progressive renal dysfunction was referred to our hospital. The patient had a history of hypertension and aortic valve replacement due to severe aortic regurgitation. On presentation, the bilateral submental and right axillary lymph nodes were palpable, with no other significant symptoms, such as a fever, night sweating, or fatigue. The serum creatinine level was

[1]Department of Nephrology, Kansai Electric Power Hospital, Japan, [2]Department of Rheumatology, Kansai Electric Power Hospital, Japan, [3]Department of Hematology, Kansai Electric Power Hospital, Japan and [4]Department of Diagnostic Pathology, Kansai Electric Power Hospital, Japan

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Correspondence to Dr. Naohiro Toda, natoda@kuhp.kyoto-u.ac.jp

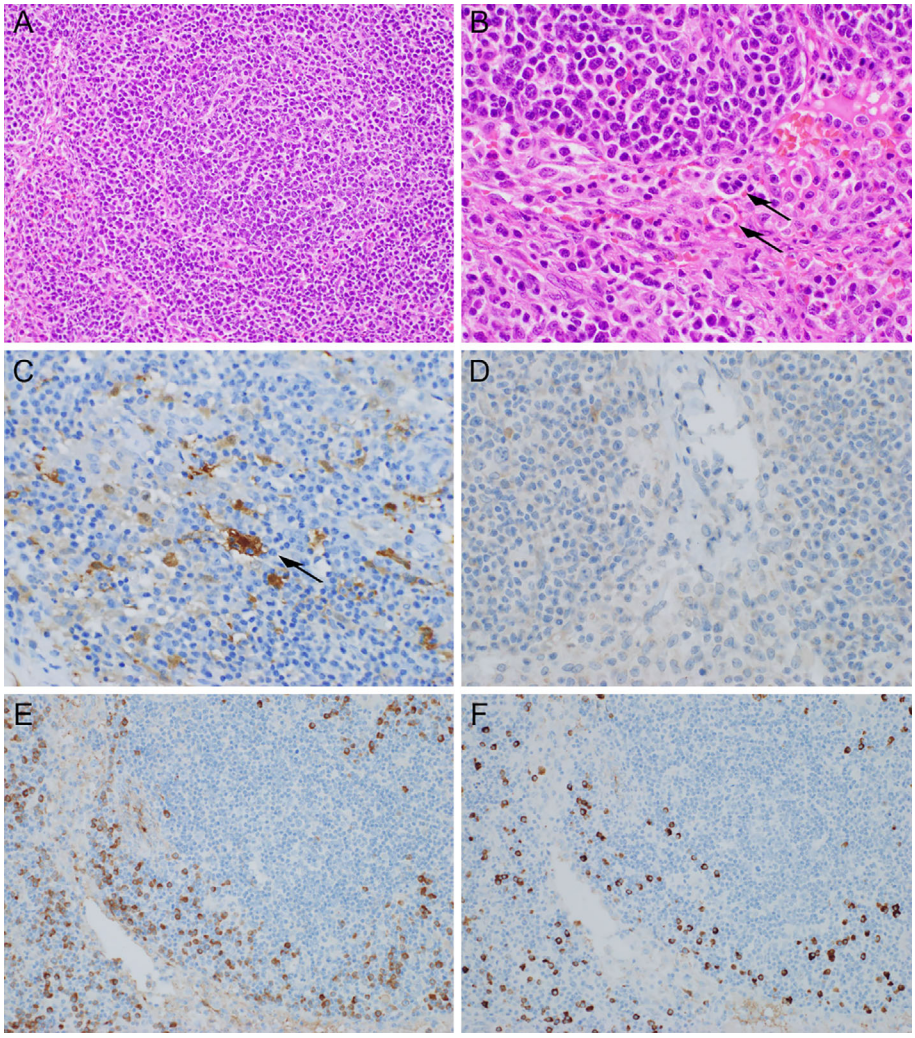

Figure 1. **Lymph node biopsy findings. Hematoxylin and Eosin staining shows the sinus expansion of large histiocytic cells with normochromatic nuclei and pale cytoplasm with diffuse infiltration of plasma cells around the lymph follicle. (B) The cytoplasm of a large histiocyte contains small lymphocytes; this phenomenon is known as emperipolesis (arrows) (A, original magnification, ×200; B, original magnification, ×400). Immunostaining of the cell showing emperipolesis reveals that it is (C) S-100-positive (arrow pointing to emperipolesis) and (D) CD1a-negative. (C, original magnification, ×200; D, original magnification, ×400). IgG-positive (E) and IgG4-positive (F) plasma cell proliferation can be observed. The IgG4/IgG-positive plasma cell ratio is 41.7%, but storiform fibrosis and vasculitis, which are typical of IgG4-RD, are not evident.**

elevated from a baseline of 0.88 mg/dL to 1.80 mg/dL. At the time of referral, serum IgG was elevated to 3,931 mg/dL; specifically, IgG4 was elevated to 883 mg/dL and IgE to 648 mg/dL, while IgA and IgM levels were within the normal range. No monoclonal immunoglobulin was found. Complement C3 and C4 were decreased to 35 mg/dL and 2 mg/dL, respectively. Urinary protein excretion was 0.41 g/gCr, while urinary beta 2-micro-globulin was markedly elevated at 13,029 μg/mL. Computed tomography revealed cervical, supraclavicular, axillary, mediastinal, para-aortic, and inguinal lymph node enlargement. The bilateral kidneys were diffusely swollen with irregular borders.

A lymph node biopsy revealed sinus expansion of large histiocytic cells with normochromic nuclei and pale cytoplasm, as well as some emperipolesis, all of which are typical features of RDD. In the background, infiltration of plasma cells was prominent, while neutrophils and eosinophilia were also observed without storiform fibrosis (Fig. 1A, B). Immunostaining revealed that the sinus histiocytes were S100- and CD68-positive and CD1a-negative (Fig. 1C, D). The IgG4/IgG ratio was 42.1% (Fig. 1E, F). Based on these findings, we diagnosed nodal RDD.

A kidney biopsy revealed diffuse severe interstitial infiltration of lymphocytes, histiocytes and plasma cells with only a few residual tubules (Fig. 2A). Glomeruli showed almost no abnormalities. Interstitial fibrosis was sparse. Storiform fibrosis and obliterative phlebitis, the typical pathological features of IgG4-RD, were not confirmed (Fig. 2B). Immunofluorescence staining showed no significant deposition. An immunohistochemical analysis revealed the infiltration of

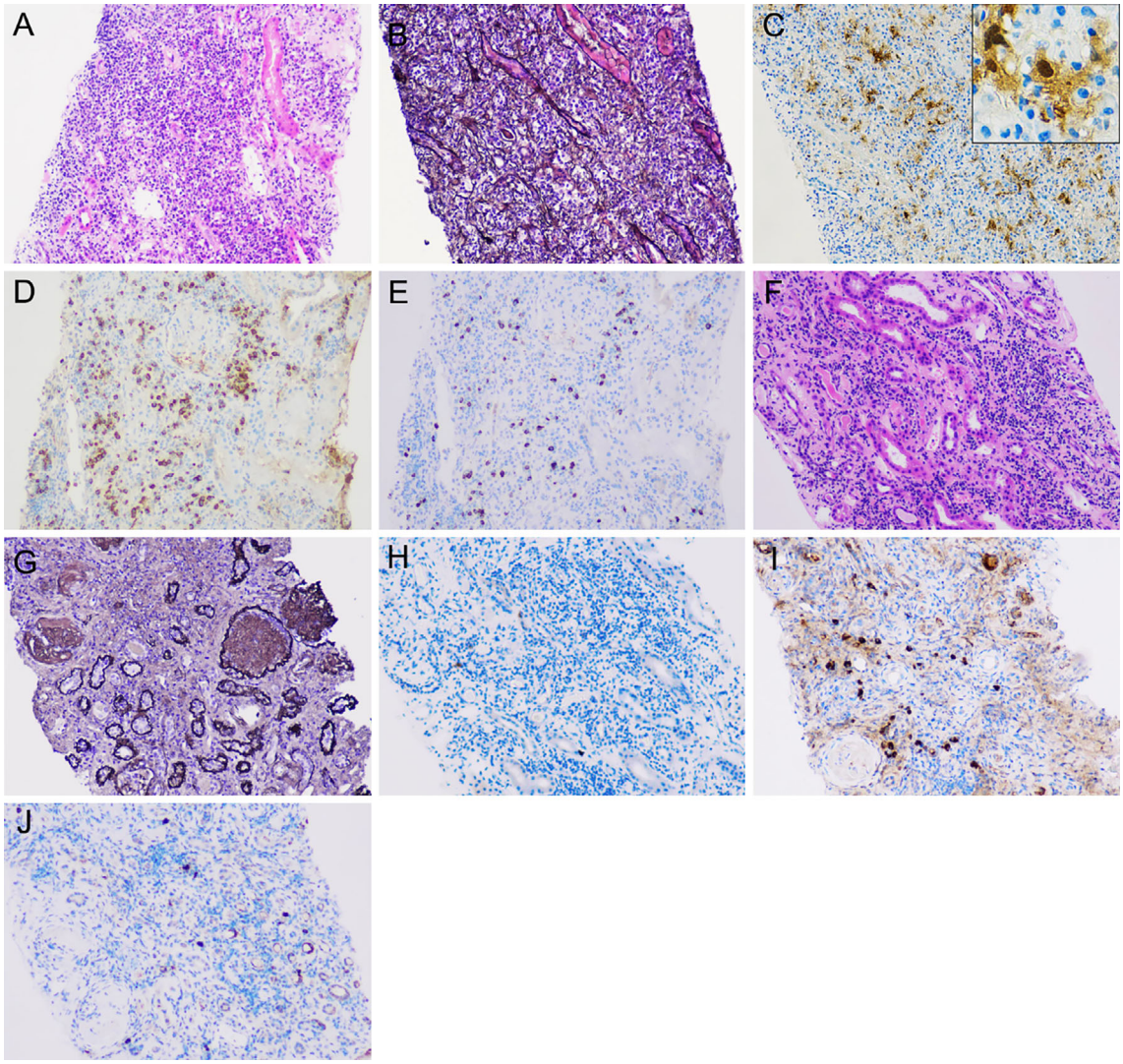

Figure 2. **Renal biopsy findings. (A-E) Findings of the initial renal biopsy. (A) Hematoxylin and Eosin (H&E) staining shows diffuse severe interstitial infiltration of inflammatory cells, and only a few residual tubules can be recognized (original magnification, ×100). (B) Periodic acid-methenamine silver (PAM) stain shows trivial fibrosis but no storiform fibrosis or obliterative phlebitis (original magnification, ×100). (C) An immunohistochemical analysis shows S100-positive histiocyte infiltration (original magnification, ×100; insert, original magnification, ×400). (D, E) An immunohistochemical analysis shows the proliferation of (D) IgG-positive plasma cells and (E) IgG4-positive plasma cells. The IgG/IgG4 ratio is 31.7%, and the number of IgG4-positive plasma cells is 91/HPF (original magnification, ×100; I, original magnification, ×100). (F-J) A repeat biopsy after oral prednisolone therapy. (F) H&E staining shows a decrease in inflammatory cells, but the patchy focal invasion of lymphocytes and plasma cells remains (original magnification, ×100). (G) shows that fibrosis has expanded, but neither storiform fibrosis nor obliterative phlebitis is observed (original magnification, ×100). An immunohistochemical analysis reveals (H) S100-positive disappearance and a decrease in (I) IgG-positive and (J) IgG4-positive plasma cells. The IgG/IgG4 ratio is 41.4%, and the number of IgG4-positive plasma cells is 15/HPF. Unexpectedly, the IgG/IgG4 ratio was higher in the repeat biopsy than in the initial biopsy (original magnification, ×100; O).**

histiocytes that were S100- and CD68-positive and CD1a-negative with no emperipolesis (Fig. 2C). The IgG4-/IgG-positive cell ratio was 38%, and the number of IgG4-positive cells was 91 cells/high-power field (HPF) (Fig. 2D, E).

The patient's clinical course is shown in Fig. 3. Because the patient became oliguric and his serum creatinine level increased to 2.48 mg/dL, 40 mg (0.7 mg/kg) of prednisolone was administered to treat tubulointerstitial nephritis. After oral prednisolone was decreased to 15 mg, his serum creatinine level improved to 1.34 mg/dL; his serum complements C3 and C4 improved to 85 and 27, respectively, while his urinary beta 2-micro-globulin level decreased to 419 μg/mL, and his lymphadenopathy disappeared.

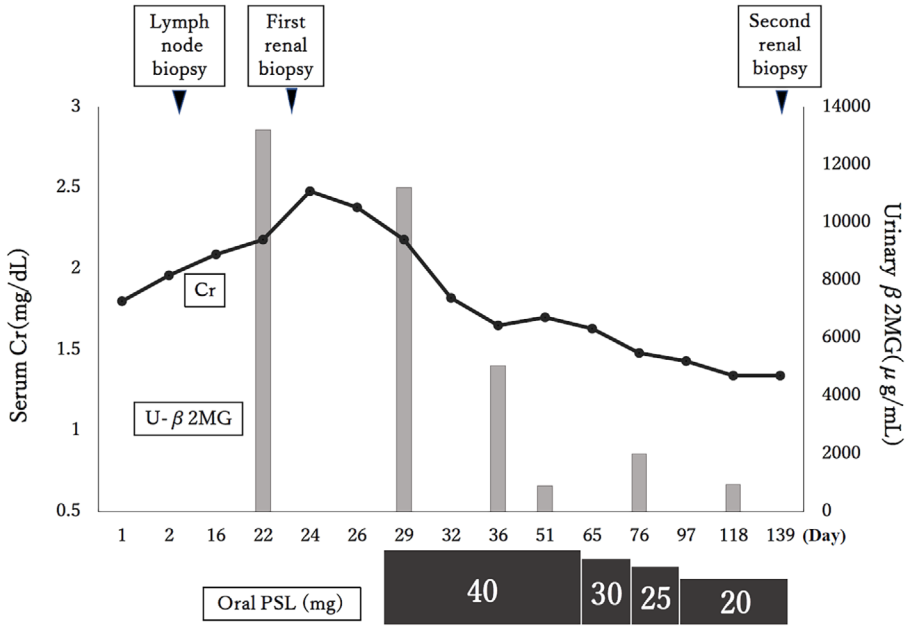

Figure 3. Clinical course. The patient's clinical course. After the administration of oral prednisolone, the serum creatinine and urinary beta 2-microglobulin levels gradually decreased. PSL: prednisolone, b2MG: b2-microglobulin

A repeat kidney biopsy was performed four months after PSL was started. Compared to the initial biopsy, the repeat biopsy showed the decreased infiltration of inflammatory cells, but the patchy focal invasion of lymphocytes and plasma cells remained (Fig. 2F), and the interstitial fibrosis had expanded (Fig. 2G). There was no emperipolesis and only a few S100-positive cells (Fig. 2H). Although the number of IgG4-positive cells decreased dramatically to 8 cells/HPF, the IgG4/IgG ratio increased to 41.4% (Fig. 2I, J). Based on the second kidney biopsy findings, we determined that the tubulointerstitial nephritis was a manifestation of extranodal RDD, not IgG4-related kidney diseases (RKD).

Discussion

We herein report a case of tubulointerstitial nephritis in RDD mimicking IgG4-RD. Although several previous reports have discussed the possibility that RDD and IgG4-RD are related, to our knowledge, this is the first report to discuss a possible association between RDD and IgG4-RD in the kidney. A 2016 revised histiocytosis classification recommends evaluating IgG4-positive plasma cell infiltration in all RDD patients and classifying them according to the presence or absence of IgG4 syndrome (6). The 2019 American College of Rheumatology (ACR)/European League Against Rheumatology classification criteria for IgG4-RD, in contrast, recommend that histiocytosis be excluded (7). Thus, the association between RDD and IgG4-RD is still controversial.

Tubulointerstitial nephritis is the most common histological finding in cases with renal involvement of IgG4-RD and is conversely rare in kidney RDD, which typically presents as a renal mass. Renal parenchymal disorder in RDD is quite rare. A few cases of severe acute kidney injury have been reported, but a renal biopsy could not be performed in most of these cases because of the deterioration of the patients' status (8, 9). There have been only two cases of biopsy-proven RDD manifesting as tubulointerstitial nephritis to date (10, 11). The first case of RDD manifesting as tubulointerstitial nephritis had S100-positive and CD1a-negative histiocytes without emperipolesis. This case was not examined for IgG4-positive plasma cell infiltration in the kidney and required etoposide for complete remission (10). The second case of RDD manifesting as tubulointerstitial nephritis was identified as IgG-RD-induced tubulointerstitial nephritis but was not examined for S100 positivity (11). That case responded adequately to steroid therapy, as did our case. This is worth noting because while RDD that does not involve the kidney typically has a benign clinical course, the prognosis of kidney RDD is considered to be poor.

Our findings suggest that RDD with a phenotype similar to that of IgG4-RD may respond well to steroid therapy. In other words, some cases that are currently diagnosed as IgG 4-RKD with lymphadenopathy may actually be RDD with tubulointerstitial nephritis. In supposed cases of IgG4-RD with massive cervical lymphadenopathy, general symptoms, such as a fever or fatigue, and other atypical clinical manifestations, we recommend a lymph node biopsy with an examination for emperipolesis and S100-positive cells to rule out the possibility of RDD with tubulointerstitial nephritis (12).

In our case, a lymph node biopsy revealed emperipolesis of some S100-positive cells, which is one of the exclusion criteria for IgG4-RD (7); this finding enabled us to diagnose nodal RDD. Other than that, however, our case had a phenotype similar to that of IgG4-RD, including elevated IgG,

IgG4, and IgE as well as hypocomplementemia. A renal biopsy in our case indicated an IgG4/IgG ratio of 38.4% and an IgG4-positive plasma cell count of 91/HPF. These findings alone were not sufficient to allow us to distinguish RDD from IgG4-RD with kidney involvement. Nevertheless, the S100-positive histiocytes in the renal biopsy suggested the infiltration of RDD into the renal parenchymal lesions. Though our renal biopsy showed no emperipolesis, scant emperipolesis is sometimes found in extranodal RDD (2). In contrast, emperipolesis has been observed in tumor lesions of extranodal RDD affecting the kidney (13). Thus, while diagnosing extranodal RDD without tumor formation can be challenging, it can sometimes be simplified by examining for S100-positive histocytes in the extranodal lesions.

The second biopsy after prednisolone therapy showed an elevated IgG4/IgG ratio and decreased numbers of S100-positive histiocytes and IgG4-positive cells. Arai et al. reported that repeat biopsies in IgG4-RKD tend to show decreased numbers of IgG4-positive cells and a reduced IgG4/IgG ratio (14), suggesting that our case was not a typical one of IgG4-RD, although the number of IgG-positive cells was decreased. In addition, storiform fibrosis, which is a characteristic feature of IgG4-RD, observed in about half of patients, was not observed in our case, even in repeat biopsy (15). Previous reports on extranodal RDD in other sites, such as the nervous system and pancreas, include no examples of IgG4-RD-mimicking patients exhibiting storiform fibrosis or obliterative phlebitis (16). Based on all of our clinical and pathological findings, we diagnosed this patient's tubulointerstitial nephritis as a manifestation of extranodal RDD as opposed to IgG4-RKD.

Classically, RDD has been considered a reactive process occurring in connection with certain inflammatory diseases. More recently, however, next-generation DNA sequencing has revealed point mutations, such as KRAS and MAP2K1 mutations, in 33% of RDD cases (17). These studies have indicated that RDD has clonality and involves activation of the MAPK pathway. Recently, the autoantibody against laminin 511-E8 was detected in patients with autoimmune pancreatitis (AIP), suggesting that IgG4-RD is an autoimmune disease (18). RDD is clearly a completely different entity from IgG4-RD, although some cases of RDD do mimic the clinical and pathological characteristics of IgG4-RD. At present, the pathological phenotype of IgG4-RD is thought to be caused by T helper 2 (Th2) and regulatory T (Treg) cells (19). Zhang et al. reported that the Treg cell counts were significantly higher in extranodal RDD tissues than in reactive lymph nodes (20). We speculate that the upregulation of IL-6 and IL-4 from Treg cells in RDD leads to the RDD phenotype that mimics IgG4-RD. Furthermore, as hypocomplementemia and elevation of IgE were seen in our case, we propose that they are induced not only in tubulointerstitial nephritis caused by IgG4-RD but also in that caused by RDD, and that they arise by the same mechanism in both conditions.

In conclusion, we encountered a case of tubulointerstitial nephritis in RDD mimicking IgG4-RD. We speculate that extranodal RDD can present as tubulointerstitial nephritis and that there may be a subset of kidney RDD that mimics IgG4-RD, as there are subsets of extranodal RDD that mimic IgG4-RD in other organs.

The authors state that they have no Conflict of Interest (COI).

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References

1. Abla O, Jacobsen E, Picarsic J, et al. Consensus recommendations for the diagnosis and clinical management of Rosai-Dorfman-Destombes disease. Blood **131**: 2877-2890, 2018.
2. Foucar E, Rosai J, Dorfman R. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): review of the entity. Semin Diagn Pathol **7**: 19-73, 1990.
3. Stone JH, Zen Y, Desphande V. IgG4-related disease. N Engl J Med **366**: 539-551, 2012.
4. Tracht J, Reid MD, Xue Y, et al. Rosai-Dorfman disease of the pancreas shows significant histologic overlap with IgG4-related diseases. Am J Surg Pathol **43**: 1536-1546, 2019.
5. Hoffmann JC, Lin CY, Bhattacharyya S, et al. Rosai-Dorfman disease of the breast with variable IgG4+ plasma cell. Am J Surg Pathol **43**: 1653-1660, 2019.
6. Emile JF, Abla O, Fraitag S, et al. Revised classification of histiocytosis and neoplasm of the macrophage-dendric cell linages. Blood **127**: 2672-2681, 2016.
7. Wallace ZS, Naden RP, Chari S, et al. The 2019 American College of Rheumatology/European League Against Rheumatology classification criteria for IgG4 related disease. Ann Rheum Dis **79**: 77-87, 2020.
8. Sasaki K, Pemmaraju N, Westin JR, et al. A single case of Rosai-Dorfman disease marked by pathologic fractures, kidney failure, and liver cirrhosis treated with single-agent cladribine. Front Oncol **4**: 297, 2014.
9. Laboudi A, Haouazine N, Benabdallah L, et al. Rosai-Dorfman disease revealed by renal failure: case report. Nephrologie **22**: 53-56, 2001.
10. Lai FM, To KF, Szeto CC, et al. Acute renal failure in a patient with Rosai-Dorfman disease. Am J Kidney Dis **34**: 1-6, 1999.
11. de Jong WK, Kluin PM, Groen HM. Overlapping immunoglobulin G4-related disease and Rosai-Dorfman disease mimicking lung cancer. Eur Respir Rev **21**: 365-367, 2012.
12. Chen LYC, Mattman A, Seidman MA, Carruthers MN. IgG4-related disease: what a hematologist needs to know. Haematologia **104**: 444-455, 2019.
13. Wang CC, Al-Hussain TO, Serrano-Olmo J, Epstein JI. Rosai-Dorfman disease of the genito-urinary tract: analysis of six cases from the testis and kidney. Histopathology **65**: 908-916, 2014.
14. Arai H, Hayashi H, Takahashi K, et al. Tubulointerstitial fibrosis in patients with IgG4-related kidney diseases: pathological findings on repeat renal biopsy. Rheumatol Int **35**: 1093-1101, 2015.
15. Saeki T, Kawano M, Nagasawa T, et al. Validation of the diagnostic criteria for IgG4-related kidney disease (IgG4-RD) 2011, and proposal of a new 2020 version. Clin Exp Nephrol **25**: 99-109, 2021.
16. Wang L, Li W, Zhang S, et al. Rosai-Dorfman disease mimicking IgG4-related disease: a single-center experience in China. Orphanet J Rare Dis **15**: 285, 2020.
17. Graces S, Medeiros LJ, Patel KP, et al. Mutually exclusive recurrent KRAS and MAP2K1 mutations in Rosai-Dorfman disease.

Mol Pathol **30**: 1367-1377, 2017.

18. Shiokawa M, Kodama Y, Sekiguchi K, et al. Laminin 511 is a target antigen in autoimmune pancreatitis. Sci Transl Med **10**: 10, 2018.

19. Satou A, Notohara K, Zen T, et al. Clinicopathological differential diagnosis of IgG4-related disease: a historical overview and a proposal of the criteria for excluding mimickers of IgG4-related disease. Pathol Int **70**: 391-402, 2020.

20. Zhang X, Hylek MD, Vardiman J. A subset of Rosai-Dorfman disease exhibits features of IgG4-related diseases. Am J Clin Pathol **139**: 622-632, 2013.