Clinical Case Report

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Progression of immunoglobulin G4-related disease to systematic lupus erythematosus after gastric cancer surgery

A case report

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Abstract

Rationale: Immunoglobulin G4 related disease (IgG4-RD) rarely coexists with other autoimmune diseases, though we had a patient whose primary clinical problem was shifted from IgG4-RD to systemic lupus erythematosus (SLE) after gastrectomy. The present paper aimed to report pathological findings and clinical course of the patient.

Patient concerns: The patient was a male aged 74 years old with gastric cancer characterized by the following symptoms: Raynaud phenomenon, polyarthralgia, and swollen parotid glands on both sides. Before gastrectomy, laboratory examination results showed renal dysfunction, hypocomplementemia, antinuclear antibodies (ANAs) positivity, and elevated serum IgG and IgG4 levels.

Diagnosis: Based on postoperative renal biopsy showing severe plasma cell infiltration with tubulointerstitial fibrosclerosis, the patient was diagnosed with IgG4-RD. Despite significant improvement in renal function and reduction in parotid gland swelling during the postoperative follow-up period, after 7 months of the gastrectomy, anti-DNA antibody levels were increased and serositis was detected, which indicated the onset of SLE. IgG4-type ANA were also detected in the sera of the patient.

Interventions: Treatment by oral prednisolone at 30 mg/day was initiated.

Outcomes: Pericardial fluid, pleural effusions, and thickening of the gallbladder wall improved after 3 months of treatment according to computed tomography.

Lessons: This study presented a rare case of comorbidity, wherein the patient's primary problem progressed from IgG4-type ANA-positive IgG4-RD to SLE after excision of gastric cancer.

Abbreviations: ANAs = antinuclear antibodies, Cr = creatinine, CT = computed tomography, IgG4-RD = immunoglobulin G4-related disease, IgG4-RKD = immunoglobulin G4-related kidney disease, PSL = prednisolone, SLE = systemic lupus erythematosus.

Keywords: anti-nuclear antibody, IgG4-related disease, systemic lupus erythematosus

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Consent to publication: The patient provided written informed consent for this study.

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1. Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a systemic condition in which IgG4-positive plasma cell infiltration and fibrosis cause organ swelling and the development of nodular and thickened lesions,[1] leading to a wide variety of clinical presentations. The diagnostic criteria for IgG4-RD, as proposed by the Japanese Ministry of Health, Labour and Welfare IgG4-RD Research Committee,[1] state that autoimmune diseases must be excluded. Generally, no disease-specific autoantibodies are detected in IgG4-RD, and therefore, the condition can easily be differentiated from systemic lupus erythematosus (SLE). Furthermore, in IgG4-RD, excessive plasma cell infiltration is detected and characteristics of sclerotic fibrosis are observed. Here, we report a male patient with gastric cancer in whom IgG4-RD progressed to SLE after gastrectomy.

2. Case report

2.1. Patient concerns

A 74-year-old male patient presented with 1-year history of illness, including Raynaud phenomenon and polyarthralgia. Preoperative laboratory examination of gastric cancer identified

Table 1

Laboratory test results of the patient on hospital admission.

	Result	Reference range
Urinalysis		
pH	5.5	4.5–8.5
Protein	±0.174 g/gCr	–
Sugar	–	–
OB	–	–
Sed. RBC	0–2/10 HPFs	1–4/HPF
Sed. WBC	2–4/10 HPFs	1–4/HPF
NAG	6.7 U/L	11.5 > U/L
α_1MG	18.8 mg/L	1.0–15.5 mg/L
β_2MG	1616 μg/L	18–348 μg/L
CBC		
WBC	4900/μL	4000–9400/μL
Basophil	0%	0–1%
Eosinophil	2%	0–7%
Seg.	33%	38–58%
Ly.	59%	36–47%
Monocyte	6%	2–7%
RBC	4.00×10^6/μL	$4.10–5.47 \times 10^6$/μL
Hb	10.5 g/dL	13.3–16.9 g/dL
Ht	33.2%	38.2–48.4%
Plt	16.2×10^4/μL	$15.3–35.0 \times 10^4$/μL
Coagulation		
PT	106%	80–135%
APTT	25.3 s	26.0–39.0 s
Fib	511 mg/dL	200–400 mg/dL
Biochemistry		
T.P.	9.9 g/dL	6.7–8.3 g/dL
Albumin	39.6%	60–7–71.3%
α1	2.3%	1.9–2.9%
α2	8.2%	6.1–9.6%
β	4.6%	7.0–10.5%
γ	45.3%	10.3–20.4%
ALB	3.5 g/dL	4.0–5.0 g/dL
AST	18 U/L	13–33 U/L
ALT	11 U/L	6–30 U/L
LDH	144 U/L	119–229 U/L
γGTP	18 U/L	10–47 U/L
Amy	120 U/L	37–125 U/L
CK	48 U/L	62–287 U/L
BUN	22.9 mg/dL	8.0–22.0 mg/dL
UA	8.7 mg/dL	3.6–7.0 mg/dL
Cr	1.38 mg/dL	0.6–1.1 mg/dL
Na	137 mEq/L	138–146 mEq/L
K	3.8 mEq/L	3.6–4.9 mEq/L
Cl	104 mEq/L	99–109 mEq/L
Ca	9.3 mg/dL	8.7–10.3 mEq/L
Pi	3.7 mg/dL	2.5–4.7 mg/dL
T.Cho	167 mg/dL	128–219 mg/dL
FBS	79 mg/dL	70–109 mg/dL
HbA1c	6.5%	4.6–6.2%
CRP	0.5 mg/dL	0.3 > mg/dL
IgG	4840 mg/dL	870–1700 mg/dL
IgG4	1210 mg/dL	4.8–105 mg/dL
IgA	230 mg/dL	110–410 mg/dL
IgM	112 mg/dL	35–220 mg/dL
IgE	527 IU/ml	0–99 IU/mL
C3	37 mg/dL	86–160 mg/dL
C4	2 mg/dL	17–45 mg/dL
CH50	<14.0 U/mL	28.0–38.0 U/mL
C1q	10.4 μg/mL	3.0 > μg/mL
Autoimmunity		
RF	449 U/mL	0–20 U/mL
ANA test		
Homogenous pattern	×320<	0–19
Shaggy pattern	× 40	0–19
anti-DNA (RI)	130 U/mL	6.0 > U/mL
Anti-Sm	1.8 U/mL	5 > U/mL
Anti-RNP	6.1 U/mL	5 > U/mL
Anti-SS-A	118 U/mL	7 > U/mL
Anti-SS-B	1.9 U/mL	7 > U/mL
Anti-CCP	0.7 U/mL	4.5 > U/mL

(*continued*)

Table 1

(continued).

α1 = antitripsin, α_1MG = alpha-1-microglobulin, α2 = alpha 2-microglobulin, β_2MG = beta-2-microglobulin, γGTP = gamma-glutamyl transpeptidase, ALB = albumin, ALT = alanine transaminase, ANA = antinuclear antibody, APTT = activated partial thromboplastin time, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CBC = complete blood count, CK = creatine kinase, CRP = C-reactive protein, FBS = fasting blood sugar, Fib = fibrinogen, LDH = lactate dehydrogenase, Ly = lymphocyte, NAG = N-acetylglutamate, OB = occult blood, PT = prothrombin time, RBC = red blood cells, RF = rheumatoid factor, Seg = segmented neutrophil, T.Cho = total cholesterol, T = T cells, TP = total protein, UA = uric acid, WBC = white blood cells, B = B cells.

renal dysfunction, hypergammaglobulinemia, and positive antinuclear antibody.

2.2. Clinical findings

On admission, the patient (height, 162 cm; weight, 65 kg) was hypertensive (173/86 mmHg; heart rate, 79 bpm) but did not have fever (temperature, 36.5 °C). Physical examination revealed swelling of the parotid and submandibular glands, and axillary and inguinal lymph nodes were palpable on both sides. Serological test results revealed hypocomplementemia, increased total protein/albumin ratio, and elevated levels of creatinine (Cr) and serum IgG, IgG4, and IgE (Table 1). Immunological test results were positive for rheumatoid factor and antinuclear antibodies (ANAs), including anti-DNA antibody, anti-SSA antibody, and anti-RNP antibody. Analysis of the urine indicated minor abnormalities with elevated tubular marker levels. Computed tomography (CT) revealed enlargement of the mediastinal, axillary, and inguinal lymph nodes, with bilateral lymph node enlargement extending from the para-aortic nodes to those around the celiac and common iliac arteries, whereas the kidneys did not show any enlargement. Gallium-67 scintigraphy revealed uptake in both parotid glands, shoulder joints, and knees but only in the right wrist (Fig. 1A). Axillary lymph nodes biopsy showed lymphoplasmacytic infiltration and revealed no evidence of metastasis. The patient had been classified into stage IIIa gastric tubular adenocarcinoma, and then underwent distal gastrectomy. After this gastrectomy, he was diagnosed with the stage IIIa with pT4aN1M0. The patient's timeline is described in Figure 2.

2.3. Diagnostic focus and assessment

Renal biopsy was performed 2 months after gastrectomy. Light microscopy revealed excessive plasma cell infiltration and diffused tubulointerstitial fibrosclerosis in the involved regions, which were clearly delineated from uninvolved regions (Fig. 1B and C). In addition, some lesions extended into the capsule (Fig. 1D). The glomerulus showed no proliferative changes or basement membrane abnormalities in the glomeruli (Fig. 1E). Immunohistochemistry showed marked IgG4-positive plasma cell infiltration in the tubulointerstitium, with the ratio of IgG4-/

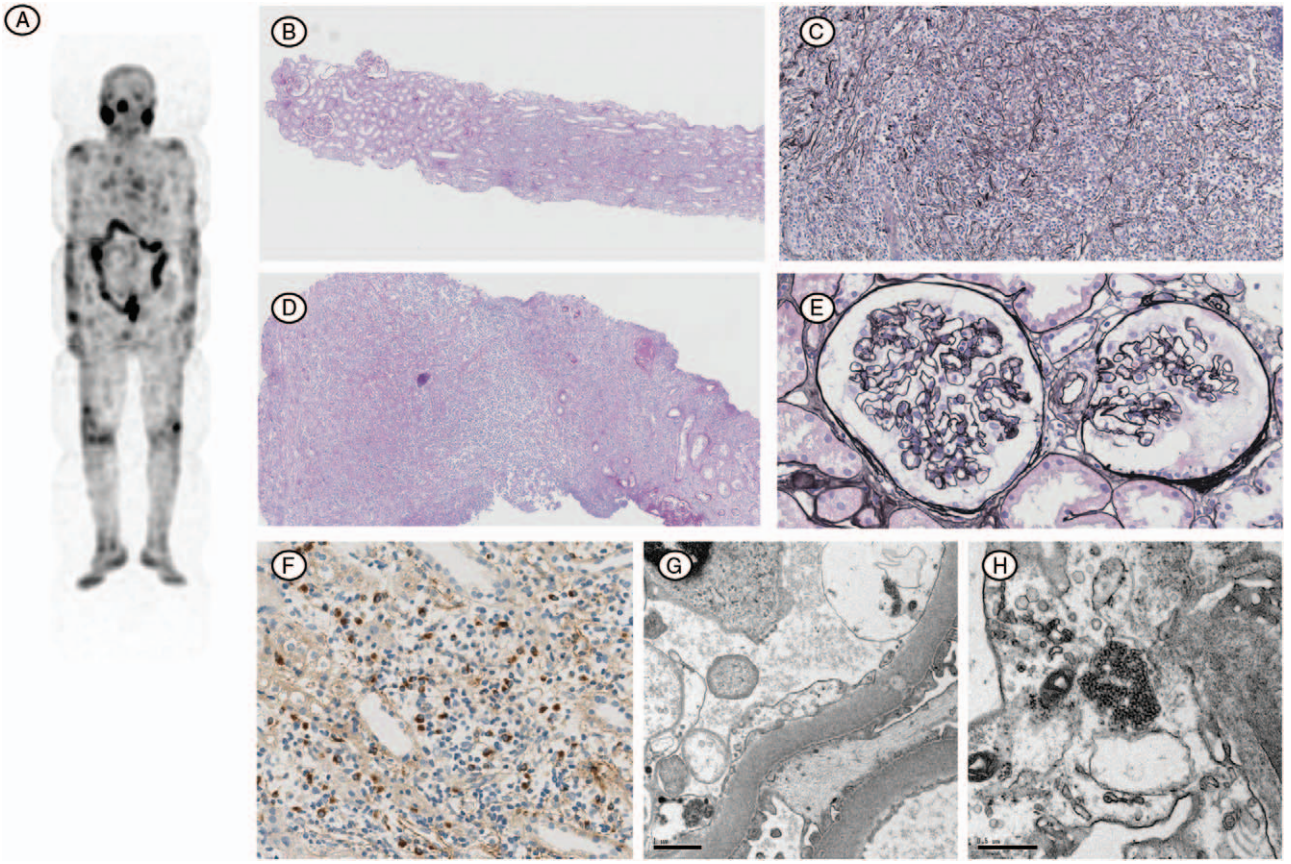

Figure 1. (A) Gallium-67 scintigraphy. (B)–(H) Light microscopy and electron microscopy findings from kidney biopsy specimens. Gallium uptake was evident in the bilateral parotid glands, shoulders, right wrist, and knees, but no uptake was noted in the kidneys. (B)–(H) Light microscopy and electron microscopy findings from kidney biopsy specimens. Involved and uninvolved regions are clearly demarcated (B: periodic acid-Schiff stain, × 50), and bird's eye fibrosis is observed in the interstitium (C: periodic acid-methenamine-silver stain, × 200). Cellular infiltration extended to the capsule (D: periodic acid-Schiff stain, × 100). Glomerular abnormalities were minor (E: Periodic acid-methenamine-silver stain, × 400). IgG4 immunostaining revealed large numbers of IgG4-positive plasma cells (IgG4/IgG-positive cells > 40%) (× 200). Electron microscopy did not show any electron-dense deposits, and microtubular structures were present within endothelial cells (G, H).

IgG-positive cells being > 40% (Fig. 1F). Unfortunately, specimens for immunofluorescence studies did not contain any glomeruli. However, mild granular positive staining of IgG, IgA, and C1q were localized in the tubular basement membrane. Electron microscopy did not reveal any electron-dense deposits in glomeruli, but endothelial tubuloreticular inclusions, which are typical for lupus nephritis, were observed. (Fig. 1G and H).

We reevaluated the specimens of axillary lymph nodes that were obtained before the surgery, and observed the presence of numerous plasma cells among the follicles of which > 40% were IgG4-/IgG-positive plasma cells. Based on the diagnostic criteria and the results of renal biopsy and axillary lymph nodes biopsy, the patient was diagnosed with IgG4-RD[1] including IgG4-related kidney disease (IgG4-RKD).[2]

2.4. Therapeutic intervention, follow-up, and outcomes

Although we informed the patient about the IgG4-RD diagnosis, the patient declined corticosteroid treatment of IgG4-RD. Over the next 3 months, the parotid gland swelling and renal function spontaneously improved (Fig. 3A). Seven months after gastrectomy, the patient developed fever and dyspnea associated with elevated anti-DNA antibody levels (Fig. 3A). Furthermore, the patient's serum Cr and C-reactive protein levels were elevated. CT revealed pericardial fluid, pleural effusions, and gallbladder wall thickening (Fig. 3B). The patient thus met 4 (namely arthritis, serositis, positivity for anti-DNA antibody, and ANA) of the 11 SLE classification criteria as established by the American College of Rheumatology in 1997. Serositis rapidly resolved following administration of oral prednisolone (PSL) at 30 mg/day (0.5 mg/kg body weight). Renal function improved approximately 1 month after initiating the treatment (Fig. 3A). Pericardial fluid, pleural effusions, and gallbladder wall thickening improved after 3 months of treatment, as observed on CT (Fig. 3B). Furthermore, CT performed 1 year after initiating corticosteroid treatment revealed mild atrophy of both the kidneys, which is consistent with the long-term course of IgG4-RKD (Fig. 3B).

The observations, therefore, suggest a progression of IgG4-RD to SLE in the patient. IgG4-type ANA is rarely detected in the sera of patients with systemic autoimmune diseases such as SLE.[3] Since the progression of IgG4-RD to SLE is rare, we assessed IgG subclasses of ANA based on a previously described method.[3] IgG4-type ANA with a shaggy pattern was detected in the sera of our patient by indirect immunofluorescence (Fig. 4).

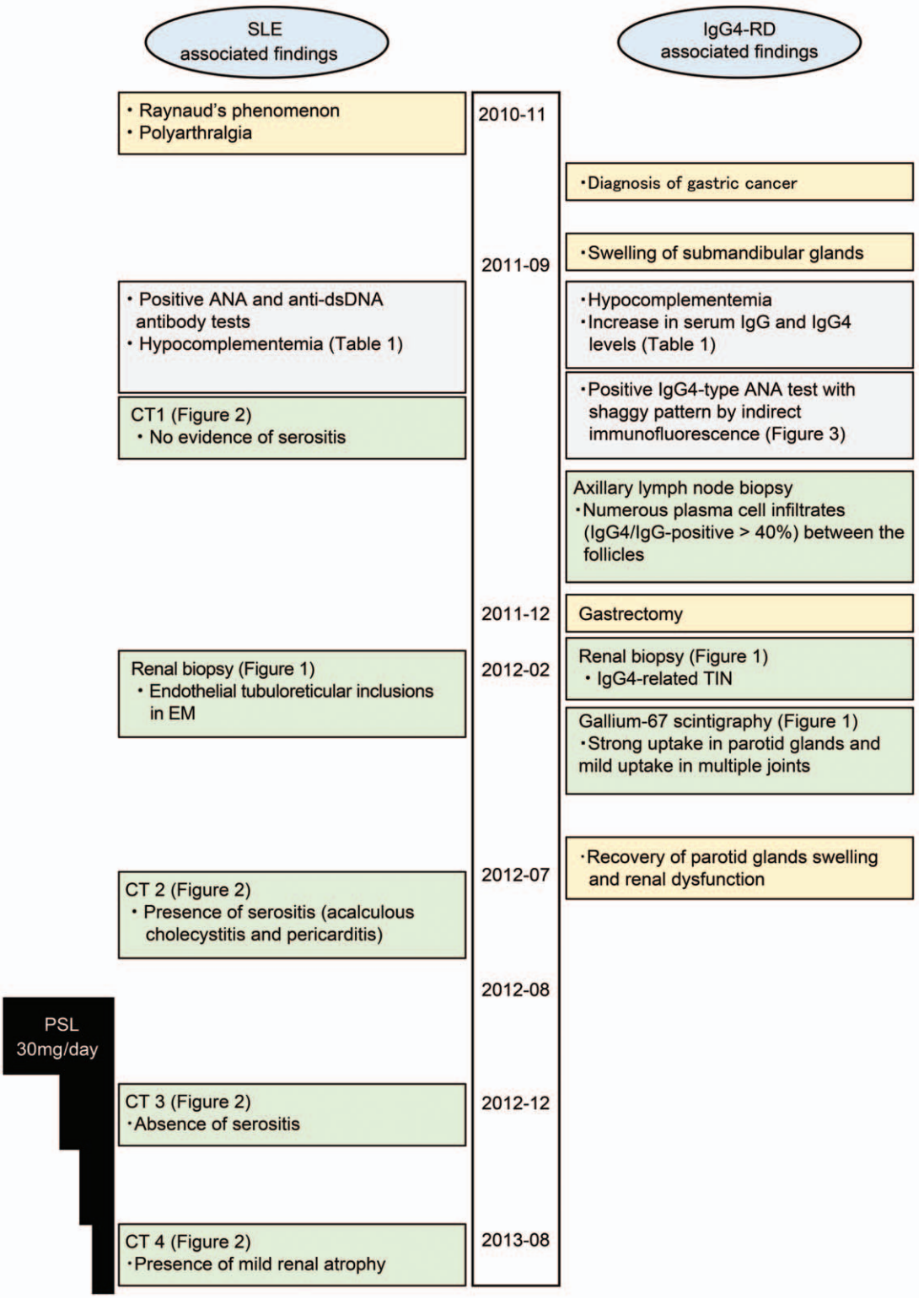

Figure 2. Patient timeline. ANA = antinuclear antibody, CT = computed tomography, EM = electron microscopy, IgG4-RD = IgG4-related disease, PSL = prednisolone, SLE = systemic lupus erythematosus, TIN = tubulointerstitial nephritis.

At the time of writing this report, that is, approximately 4 years after initiating the treatment, the patient is on a maintenance dose of 4 mg/day PSL, and no subsequent disease flare-up has been observed.

3. Discussion

Here, we present a case where the patient's main clinical presentation shifted from IgG4-RD to SLE after gastrectomy. Clinical features of IgG4-RD, including hypergammaglobuline-

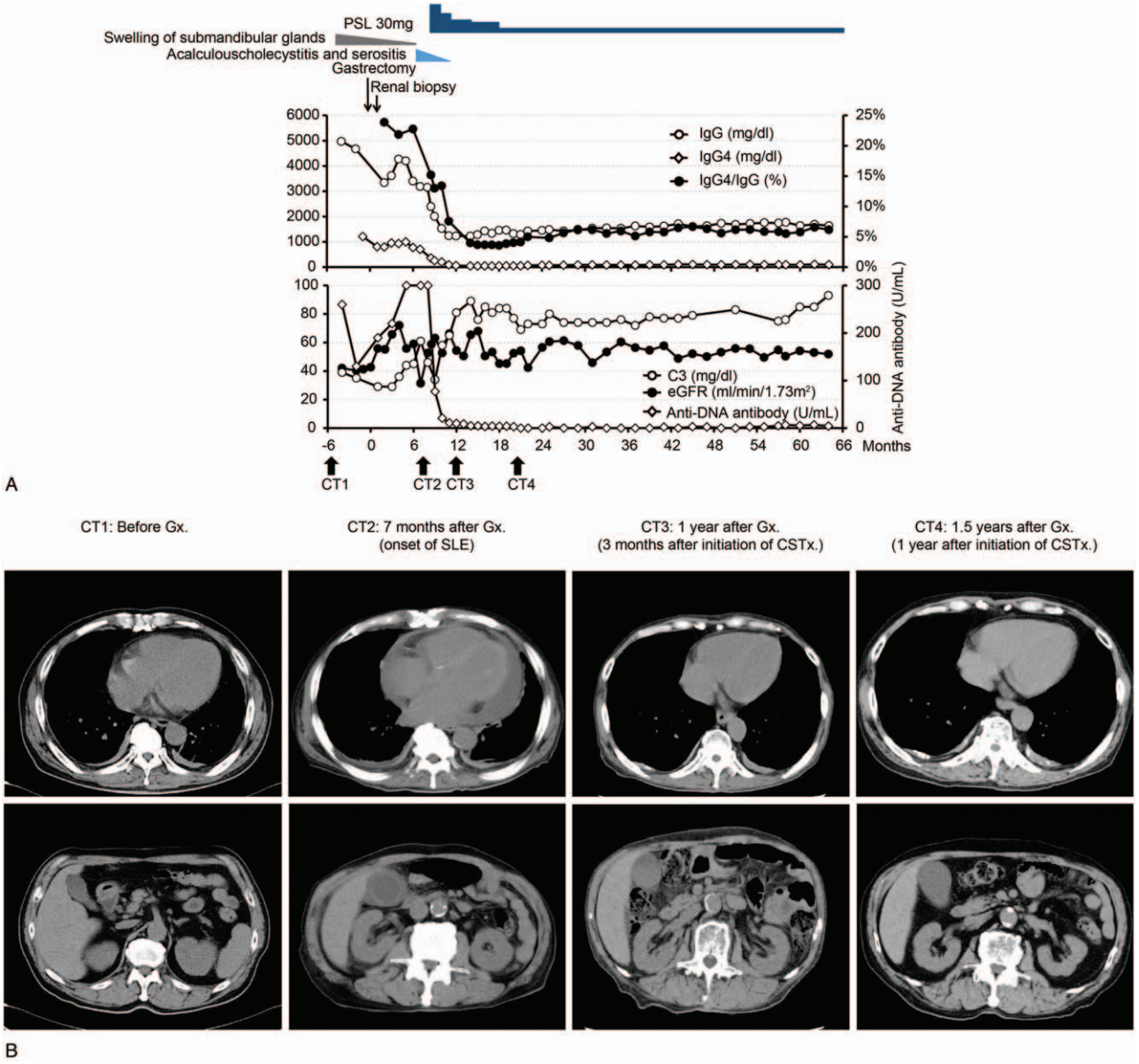

Figure 3. (A) Clinical course of the patient. (B) Sequential chest and abdominal computed tomography (CT) scans. Pericardial fluid and thickening of the gallbladder wall were observed 7 months after gastrectomy (Gx). Imaging findings improved rapidly after initiating corticosteroid treatment (CSTx) (PSL, 30 mg/day). Mild atrophy of both kidneys was evident on follow-up CT conducted 1 year after initiating CSTx.

mia, elevated serum IgG4 levels, positive ANA test results, and hypocomplementemia, are also observed in SLE. Approximately 50% of IgG4-RKD patients test positive for ANA [4]; however, typically, disease-specific antibodies are not detected, and IgG4-RD and autoimmune diseases rarely coexist.

Serositis often occur in conjunction with SLE and other forms of connective tissue diseases, but it has also been reported as an organ lesion in IgG4-RD.[5] Although we were unable to perform a histopathological evaluation of serositis in the present case, the fact that anti-DNA antibodies were also elevated at the same time indicated that serositis was likely due to SLE.

Several studies have investigated ANA subclasses in systemic autoimmune diseases, including SLE and IgG4-RD, and found that IgG4-type ANAs were rarely detected, suggesting that IgG4 is not preferentially used to synthesize ANA.[3,6,7] However, IgG4-type ANAs were detected in the sera of our patient. To the best of our knowledge, this is the first report to detect IgG4-type ANAs in SLE or IgG4-RD. This result suggests that IgG4-type autoantibody plays a role in the pathogenesis of this patient.

Recently, some studies have suggested that IgG4-RD has a complicated association with malignancy development[8,9] and represents a paraneoplastic state.[10] In our patient, the resection of the malignant tumor may have reduced the pathogenesis of IgG4-RD, possibly reflecting its characteristic as a paraneoplastic syndrome.

In summary, we treated a rare case of a comorbid autoimmune disease involving IgG4-RD and SLE, wherein the primary clinical condition progressed from IgG4-type ANA-positive IgG4-RD to SLE after excision of gastric cancer.

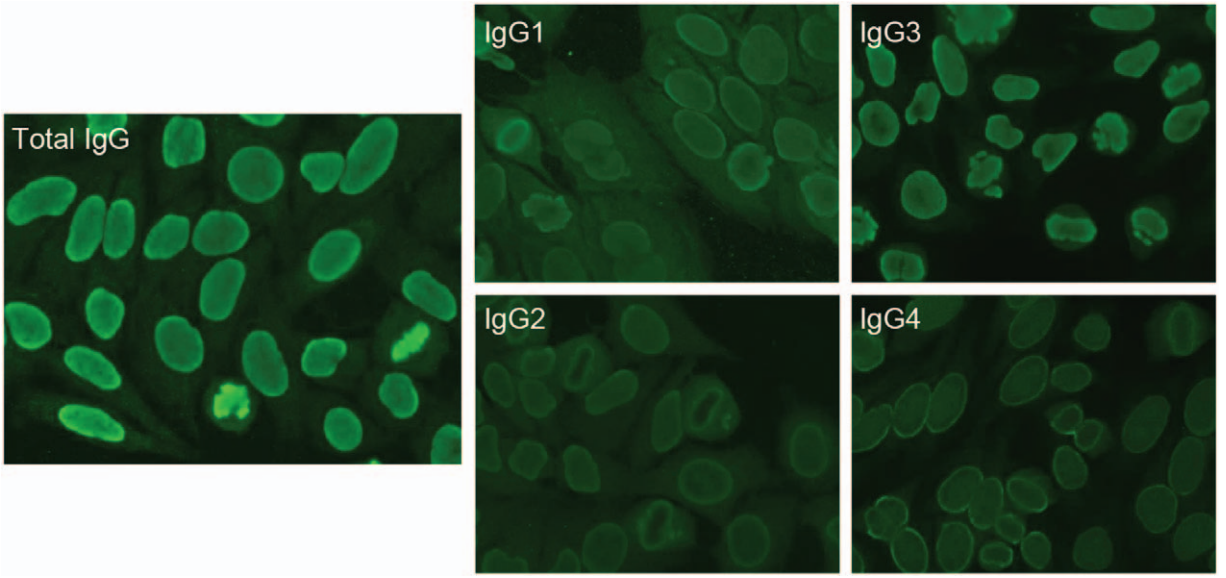

Figure 4. IgG subclasses of antinuclear antibodies (ANAs) in the patient as determined by modified indirect immunofluorescence. IgG subclasses of ANA were detected using secondary anti-human IgG1, anti-human IgG2, anti-human IgG3, or anti-human IgG4 monoclonal antibodies, followed by a reaction with Alexa Fluor 488-conjugated goat anti-mouse IgG. The patient had similar ANA patterns among IgG subclasses, as observed for total IgG. Total IgG had homogeneous, shaggy, and cytoplasmic patterns; IgG1 and IgG2 had shaggy and cytoplasmic patterns; IgG3 had homogeneous and shaggy patterns; and IgG4 had shaggy patterns only.

To the best of our knowledge, this is the first report on a patient's primary condition progressing from IgG4-type ANA-positive IgG4-RD to SLE after excision of gastric cancer.

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None.

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