SIG session (PSIR)
Case discussion

1. CASE OF COMPRESSIVE MYELOPATHY DUE TO HYPERTROPHIC PACHYMENINX

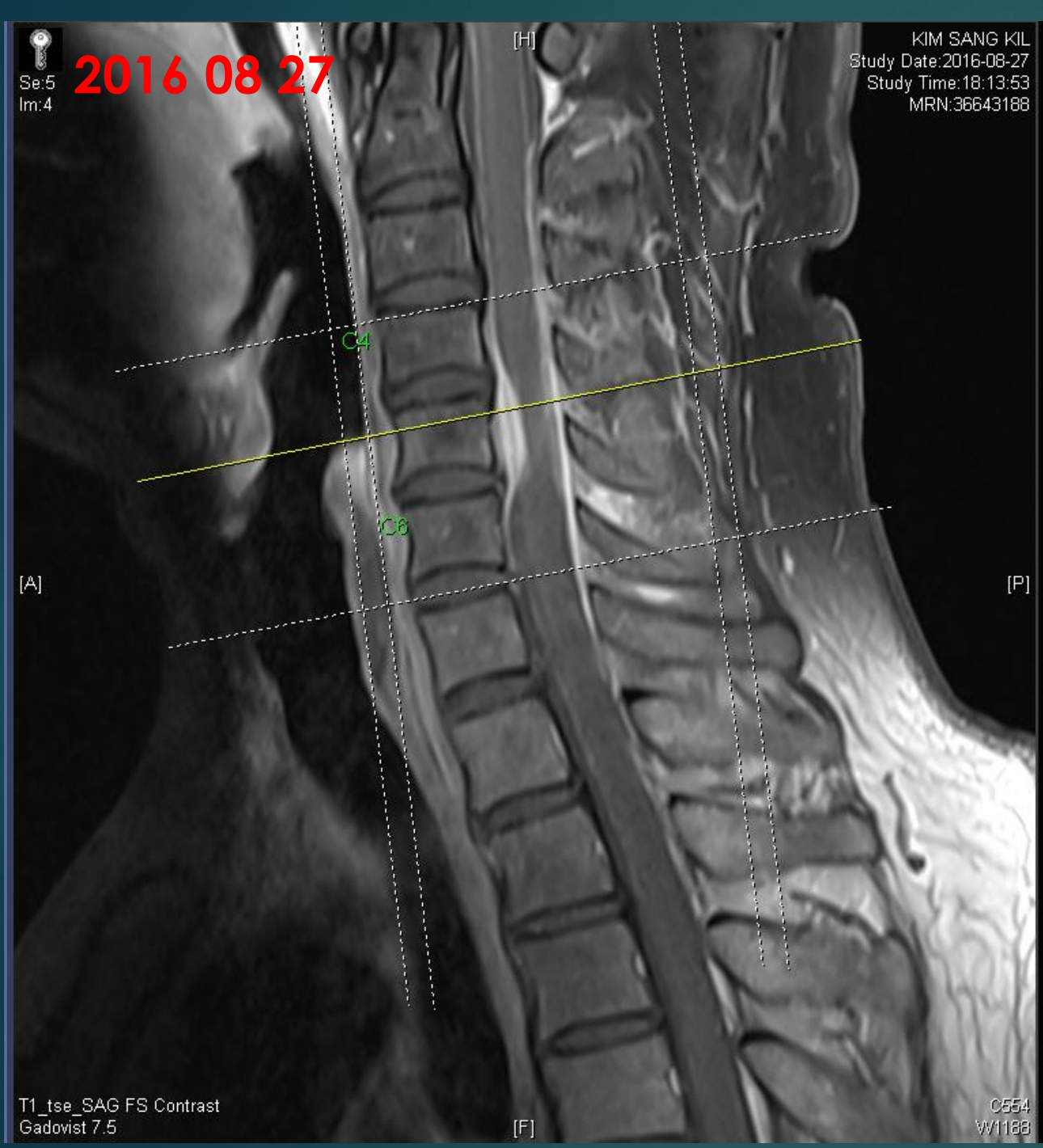
중앙 대학교 재활의학과 이병찬

Case presentation

M/41 KSK

M/41

- C. C: Lt Shoulder Pain
- 2016.08 외상 이후 좌측 어깨 통증이 지속되어 C-spine MRI를 촬영함.
- 촬영한 C-spine MRI 상 C4-6 mass r/o Spinal cord tumor가 발견되어, 2016.08.31 외래 내원함.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Study Time:18:13:53
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C4
C6
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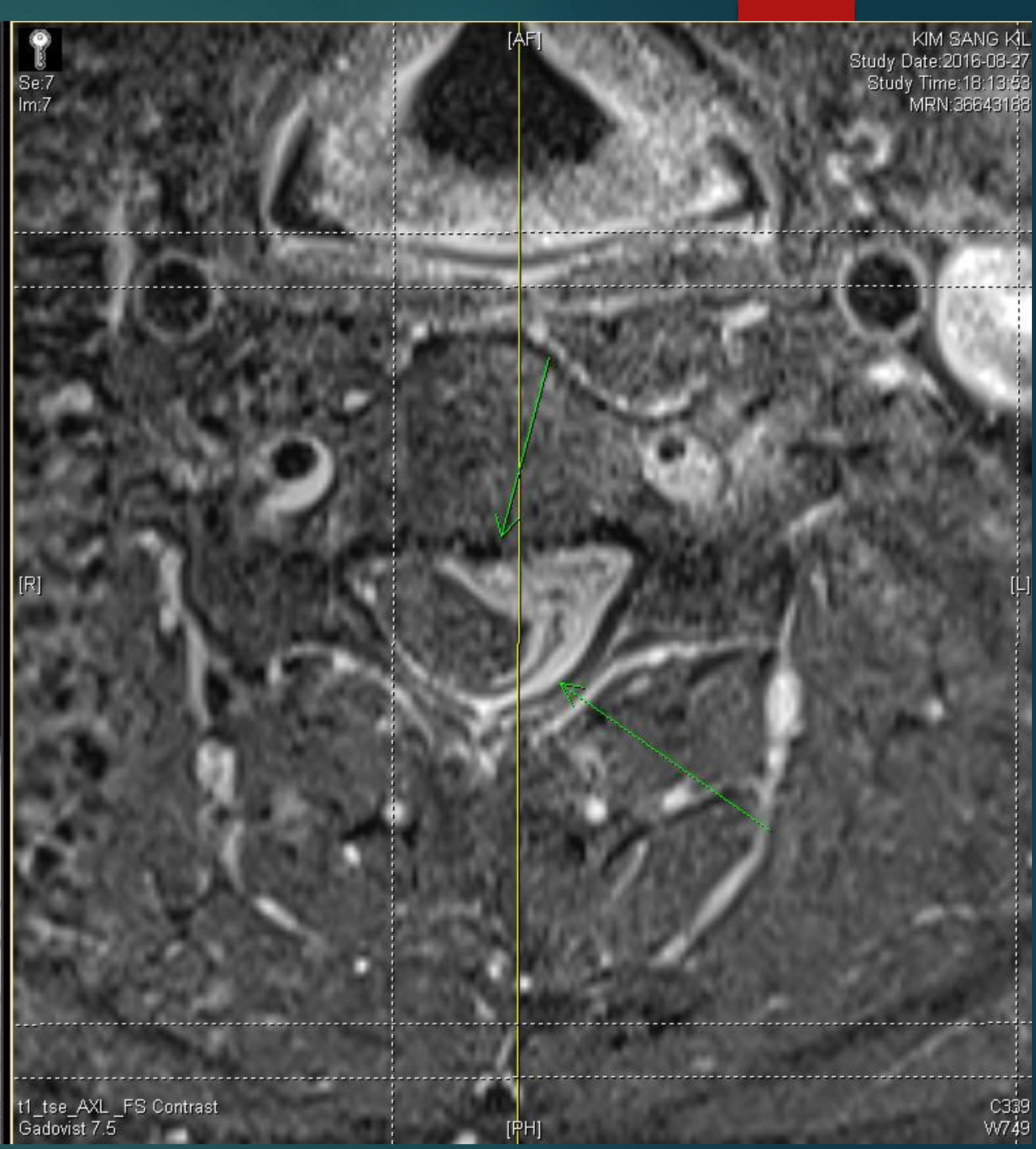
Gadovist 7.5
[F]
C554
W1188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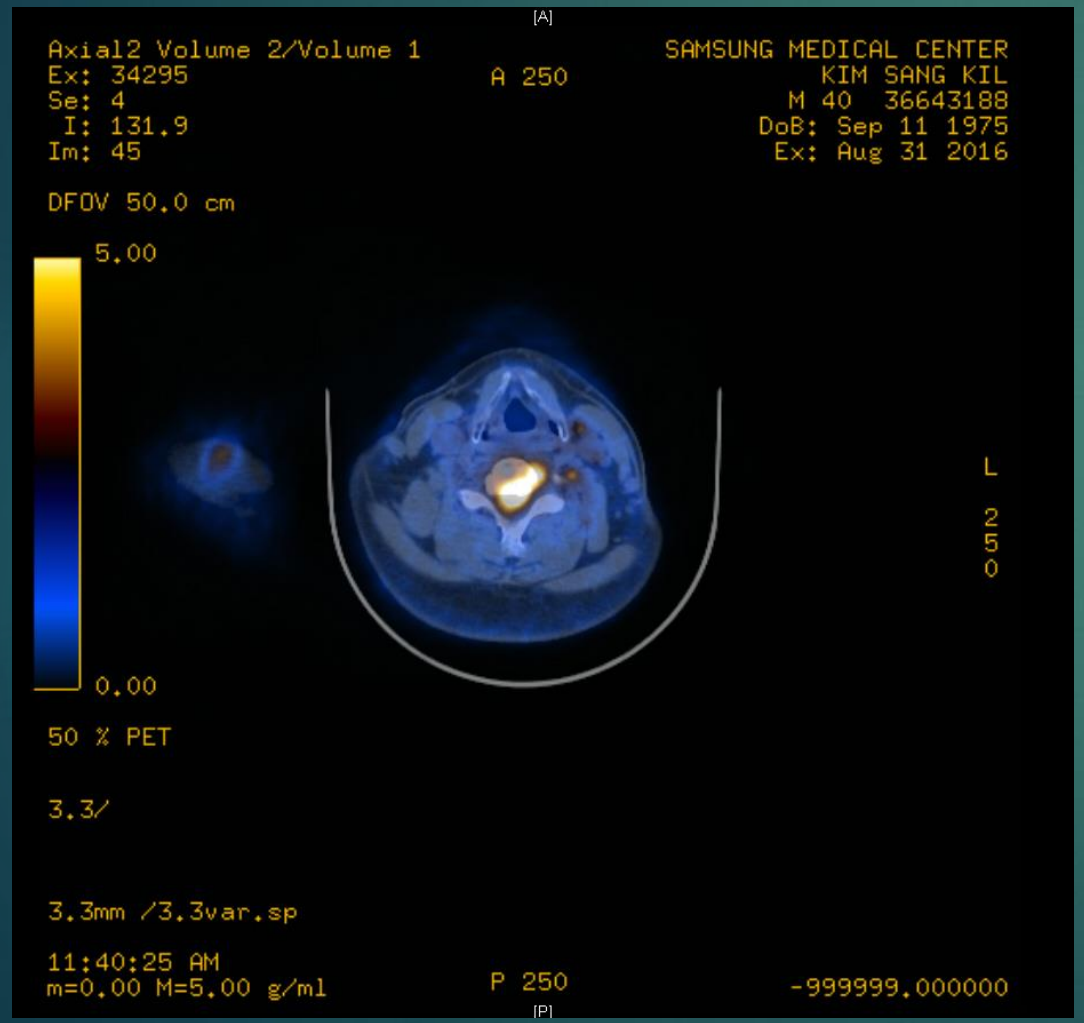
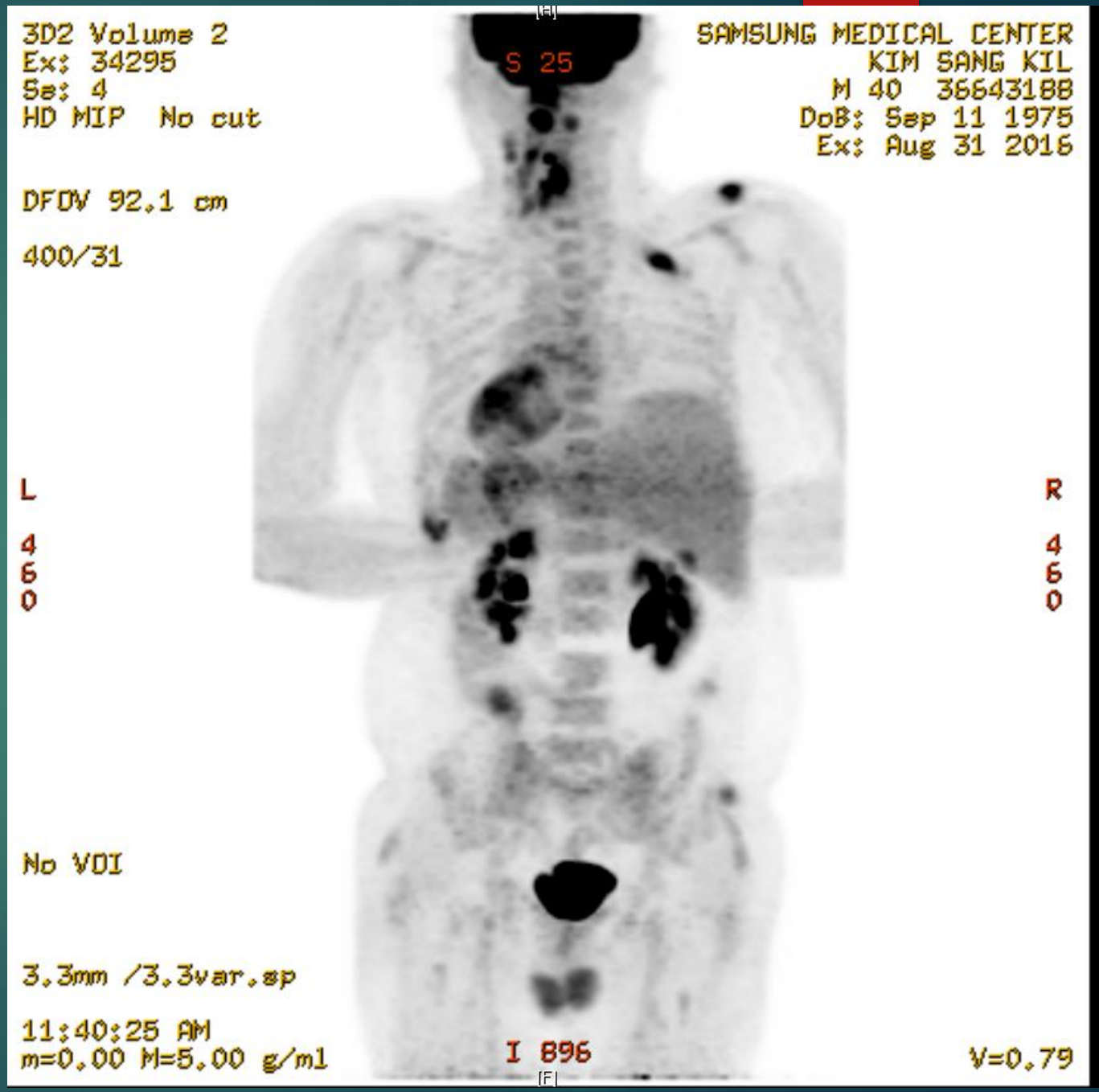
2016.08.31 PET





Assessment

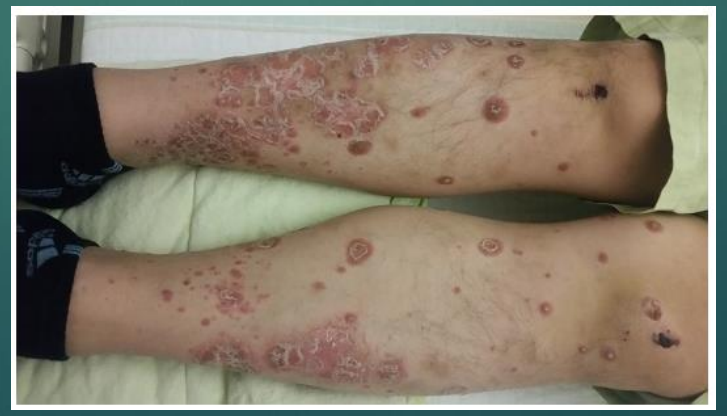
- r/o spinal cord tumor, Lt C4-6
- Abnormal FDG uptake in PET scan
  - Pharynx, cervical lymphatics, C4-6 spine, Rt pleura, clavicle, iliac bone, Lt. 7th rib and intercostal space
- r/o lymphoma, r/o hypopharyngeal cancer

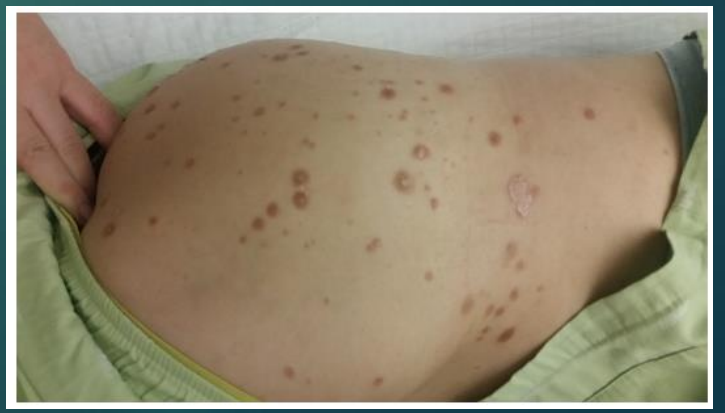
Hospital course

- 2016.09.07-2016.09.09 Dexa IV (steroid pulse)
- 2016.09.17 progression of neuropathic pain, left upper extremity weakness
- 2016.10.04 both palatine tonsillectomy 시행
  - *No evidence of malignancy*
  - Chronic active inflammation with *diffuse infiltrated lymphoplasma cells and neutrophils*.

Hospital course

- 2016.10 양측 상지 방사통 및 위약 호전 소견 보여, 관찰 지속하기로 함.
- 2016.12 몸 전반에 걸쳐 skin lesion 발생하며, 양측 상지, 하지의 방사통 심해짐. 좌측 손 사용이 어려우며, 주먹 쥐기가 어려운 소견이 관찰됨.
- 2016.12.27 양측 상, 하지의 위약이 심해지고, 중심 잡기 어려워진 소견, 소변 볼 때 abdominal strain이 필요해짐.



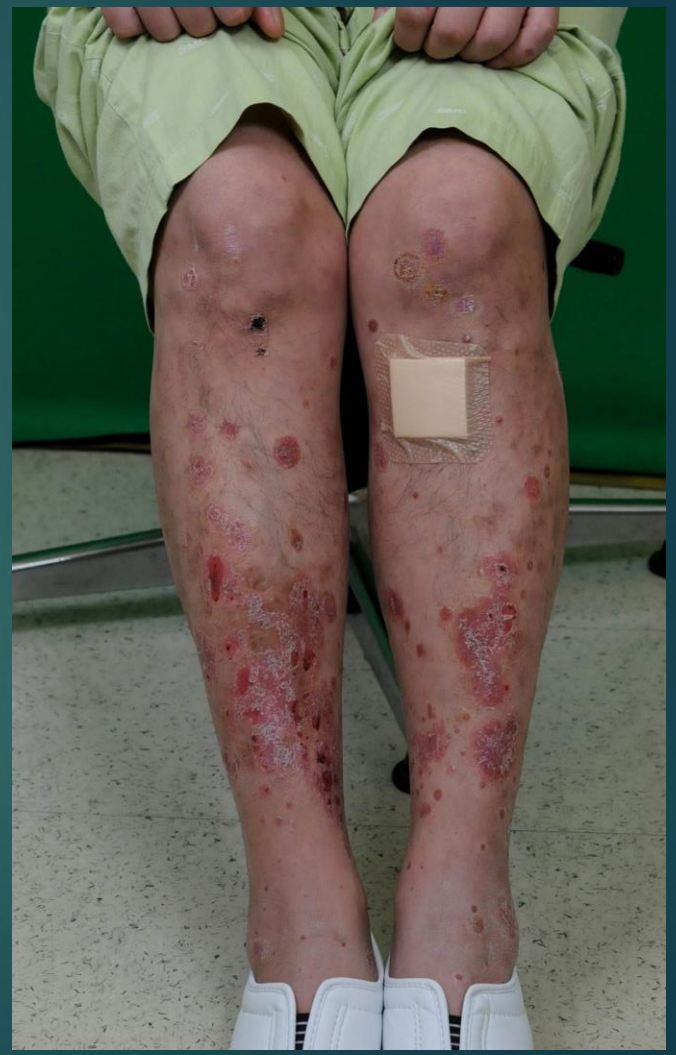


Hospital course

- 2017.01.08 tumor removal 위하여 입원, 입원 시부터 Dexamethasone IV 시작함.
- 2017.01.09 Total removal of spinal cord tumor was done

Hospital course

- 2017.01.12 Lt anterior shin skin biopsy (skin lesion site)
  - Perivascular lymphocytic infiltration, mild
  - No evidence of psoriasis, vasculitis, and panniculitis
  - IgG4: negative
- 2017.01.16 재활의학과 전과/전동



Physical examination (2017.01)

	Right	Left
Shoulder abduction	4	4-
Elbow flexion (C5)	4	3+
Wrist extension (C6)	4	3-
Elbow extension (C7)	4	4-
Wrist flexion	4	2
Finger flexion (C8)	4	3
Finger Abduction (T1)	4	3-

- Rhomberg test (+) / Tandem gait instability ++
- DTR
  - BJ + / +, TJ ++/++, BRJ ++/++
  - KJ ++/++, AJ ++/++
- Pathologic reflex
  - Babinski's reflex (-/-)
  - Hoffman sign (+/+)
  - Ankle clonus (+-/+)

Serologic evaluation

- IgG: 1314 (NR: 600-1600 mg/dl)
- IgG4: 10.8mg/dl (less than 134mg/dl)

- FANA in 1:40 positive
- ANCA : negative
- Anti-SSA/SSB : both negative

EMG/NCS

Sensory NCS

Nerve / Sites	Rec. Site	Latency ms	Amp.N-P µV	Lat. Pk ms	Amp.P-P µV
R MEDIAN - Digit II					
1. Wrist		2.90	29.9	3.65	32.2
L MEDIAN - Digit II					
1. Wrist		2.55	20.6	3.50	24.9
R ULNAR - Digit V					
1. Wrist	V	2.15	23.5	3.00	26.5
L ULNAR - Digit V					
1. Wrist	V	2.05	24.8	2.90	40.7

Motor NCS

Nerve / Sites	Lat. ms	Amp.N-P mV	Duration. ms	Area mVms	Amp.P-P mV	Cust µV	Segments	Distance cm	Velocity m/s
R MEDIAN - APB									
1. Wrist	3.45	10.2	5.80	34.0	13.1	10210.0	1 - 0		
2. Elbow	7.45	9.7	5.80	33.0	12.8	9723.3	2 - 1	23	57.5
L MEDIAN - APB									
1. Wrist	3.15	11.1	5.90	37.8	14.4	11126.7	1 - 0		
2. Elbow	7.45	11.2	6.15	38.3	14.2	11178.3	2 - 1	23	53.5
R ULNAR - ADM									
1. Wrist	2.25	8.2	6.80	33.1	12.0	8216.7	1 - 0		
2. Elbow	6.30	7.9	7.10	33.3	12.2	7911.7	2 - 1	26	64.2
L ULNAR - ADM									
1. Wrist	2.50	10.3	6.70	42.8	14.7	10285.0	1 - 0		
2. Elbow	6.20	9.5	6.75	38.8	14.0	9461.7	2 - 1	26	70.3

SEP-Upper

Protocol / Run	N1 Lat ms	P1 Lat ms	P1-N1 Amp µV
R MEDIAN			
1 Cort	20.00	23.90	3.3
2 Cort	19.90	23.90	5.2
L MEDIAN			
1 Cort	23.10	27.50	2.0
2 Cort	24.50	29.70	1.4

SEP-Lower

Protocol / Run	N0 Lat ms	P1 Lat ms	N1 Lat ms	P2 Lat ms	N2 Lat ms	P1-N0 Amp µV	N1-P1 Amp µV	N2-P2 Amp µV
R TIBIAL MALLEOLUS								
1 Cort	32.00	40.10	50.90	64.00	76.40	3.4	3.7	1.5
2 Cort	32.80	40.90	51.10	64.10	76.90	1.7	3.6	3.1
L TIBIAL MALLEOLUS								
1 Cort	36.60	42.40	51.70	64.40	76.90	1.1	3.8	1.6
2 Cort	36.00	41.00	48.10	64.50	77.30	0.57	2.4	1.8

EMG/NCS

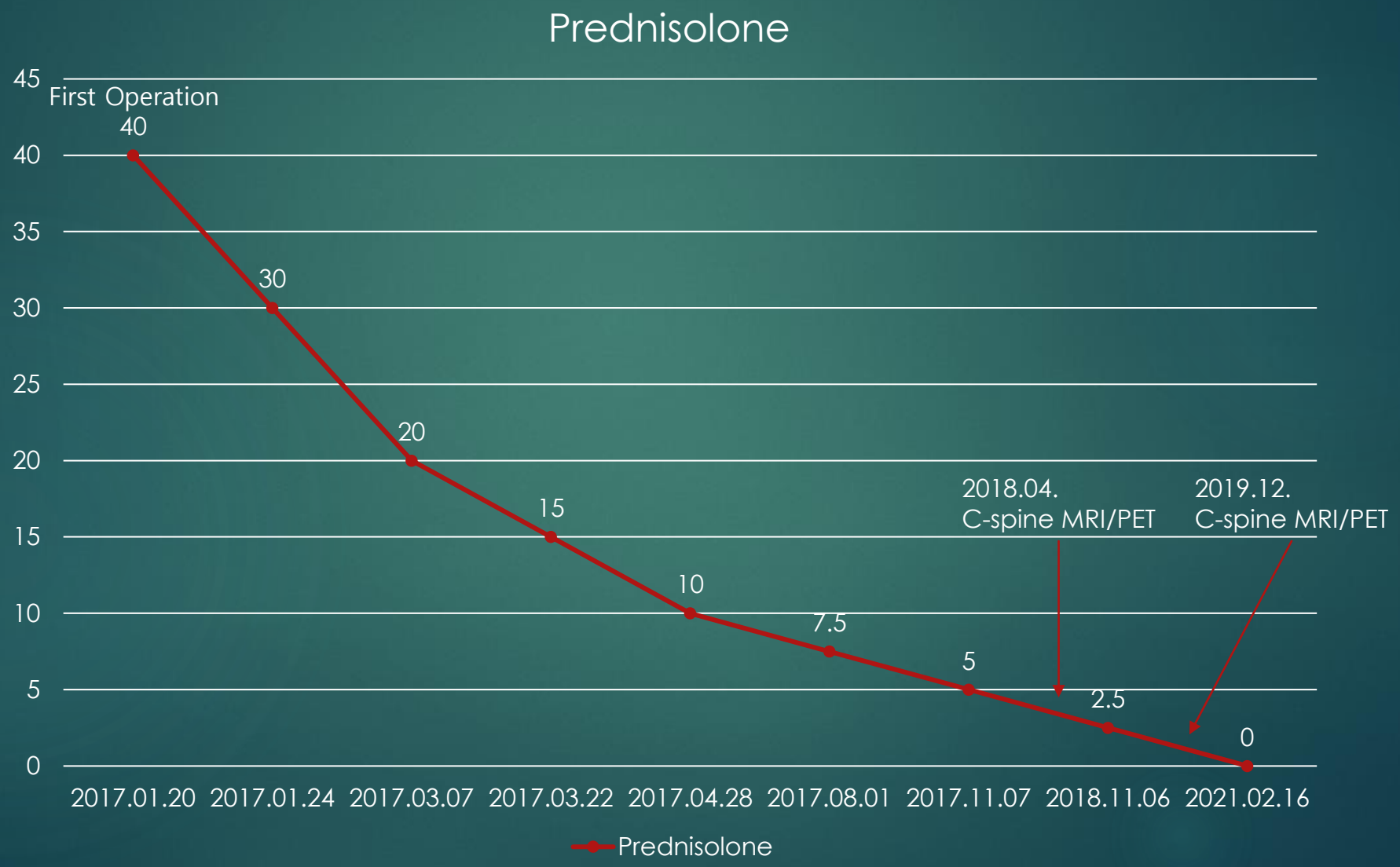
Needle EMG

EMG Summary Table											
	Spontaneous					MUAP					Recruitment
	IA	Fib	PSW	Fasc	biz	Amp	Dur.	gnt	Lpp	Spp	Pattern
R. DELTOID	N	1+	2+	None	N	N	1+	N	N	N	Reduced to double
R. BICEPS	N	None	1+	None	N	N	N	N	N	N	Reduced
R. TRICEPS	N	None	1+	None	N	N	N	N	N	N	Reduced to single
R. FLEX CARPI ULN	Increased	None	None	None	N	N	N	N	N	N	Reduced to complete
R. FLEX CARPI RAD	N	None	2+	None	N	N	N	N	N	N	Reduced
R. ABD POLL BREVIS	N	None	None	None	N	N	N	N	N	N	Reduced to complete
R. FIRST D INTEROSS	N	None	None	None	N	N	N	N	N	N	Reduced to complete
L. DELTOID	N	None	2+	None	N	N	N	N	+	N	Reduced
L. BICEPS	N	None	2+	None	N	N	N	+	N	N	Reduced
L. TRICEPS	N	1+	2+	None	N	N	N	N	N	N	Reduced to double
L. FLEX CARPI ULN	N	None	2+	None	N	N	N	N	N	N	Reduced
L. FLEX CARPI RAD	N	None	3+	None	N	N	N	N	N	N	Reduced
L. ABD POLL BREVIS	N	None	None	None	N	N	N	N	N	N	Reduced to complete
L. FIRST D INTEROSS	Increased	Poor resting				N	N	N	N	N	Reduced

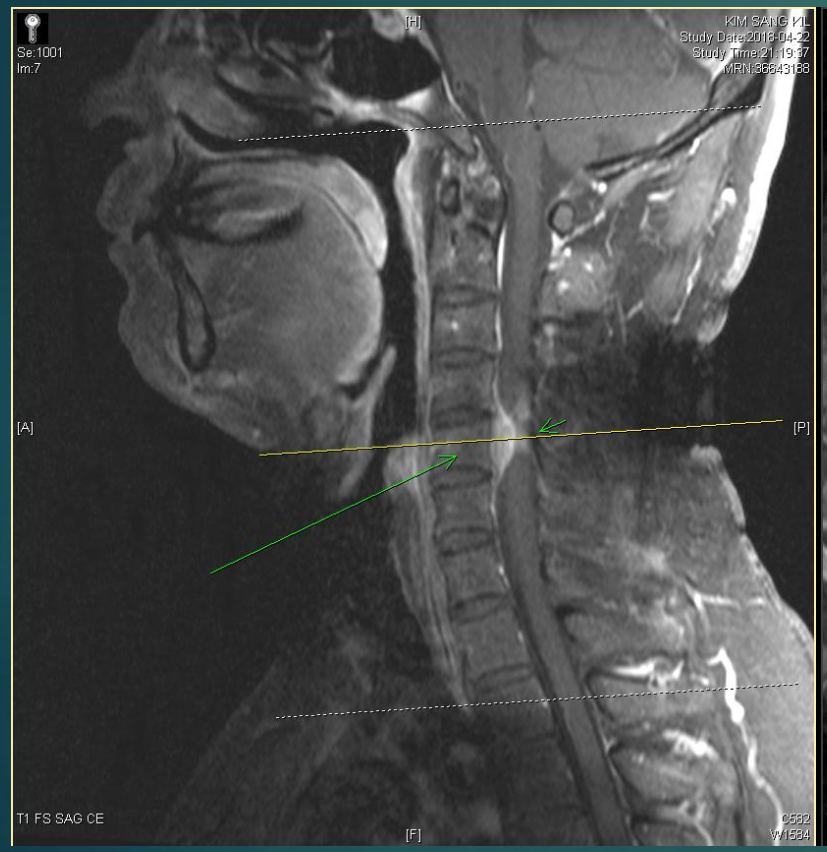
Bilateral cervical polyradiculopathy

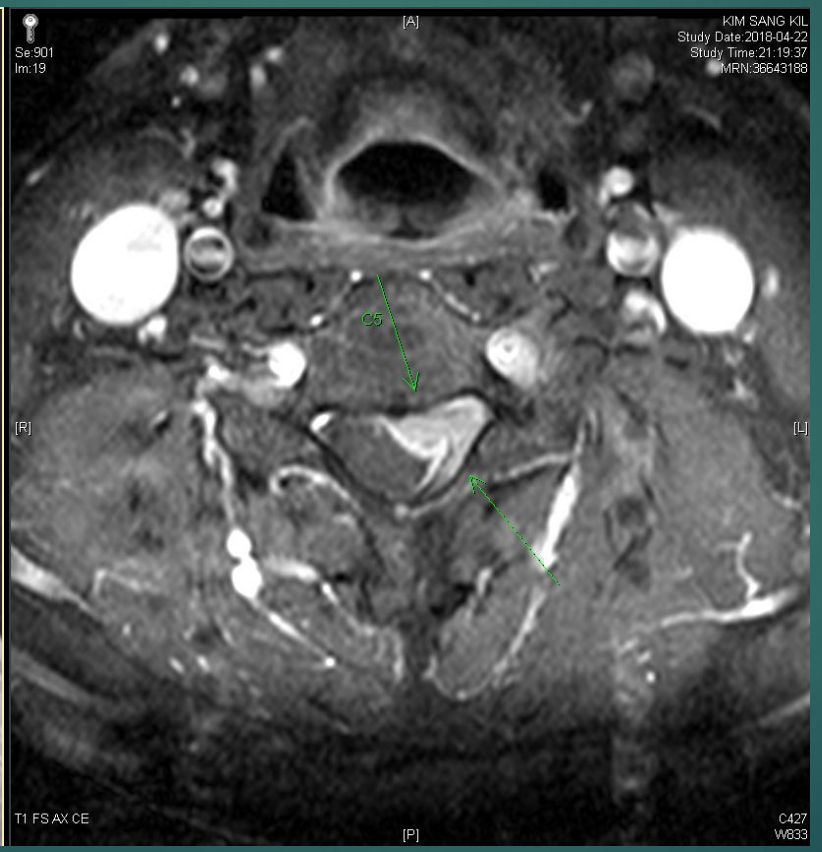
(Rt: C5-6-7, Lt: C5-6-7-8)

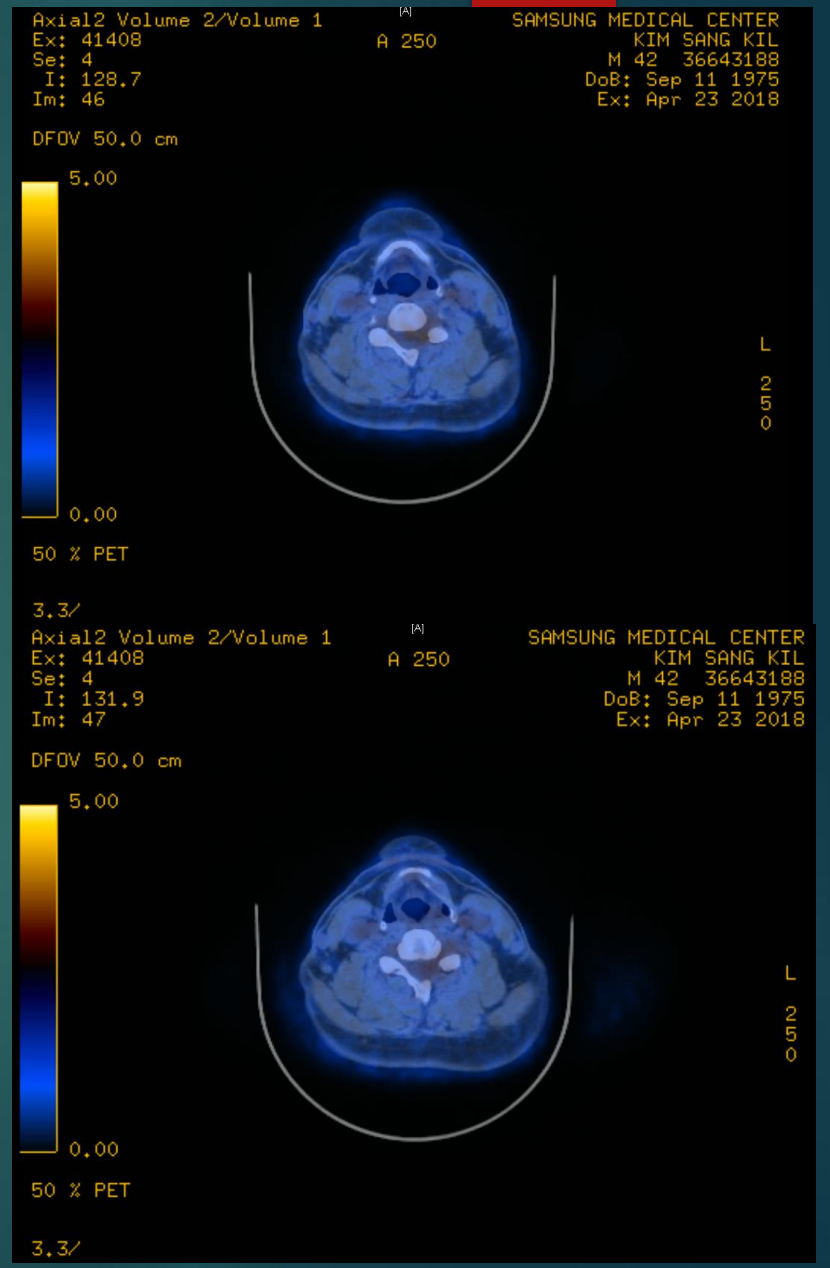
Hospital course



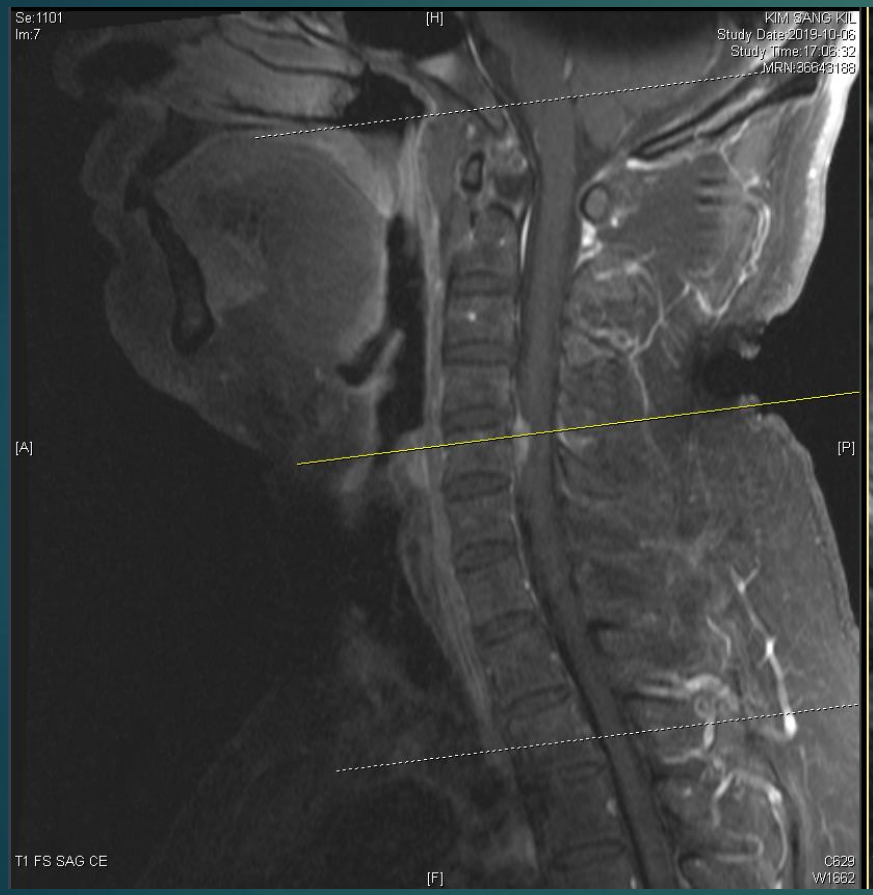
2018.04 C-spine MRI/PET

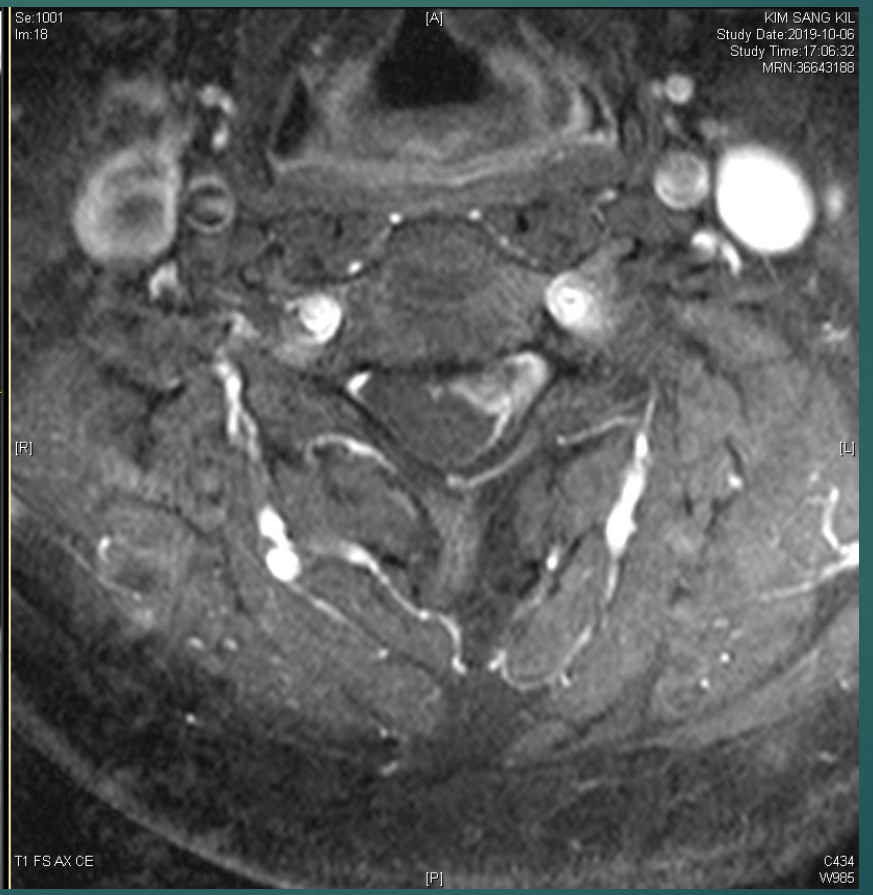


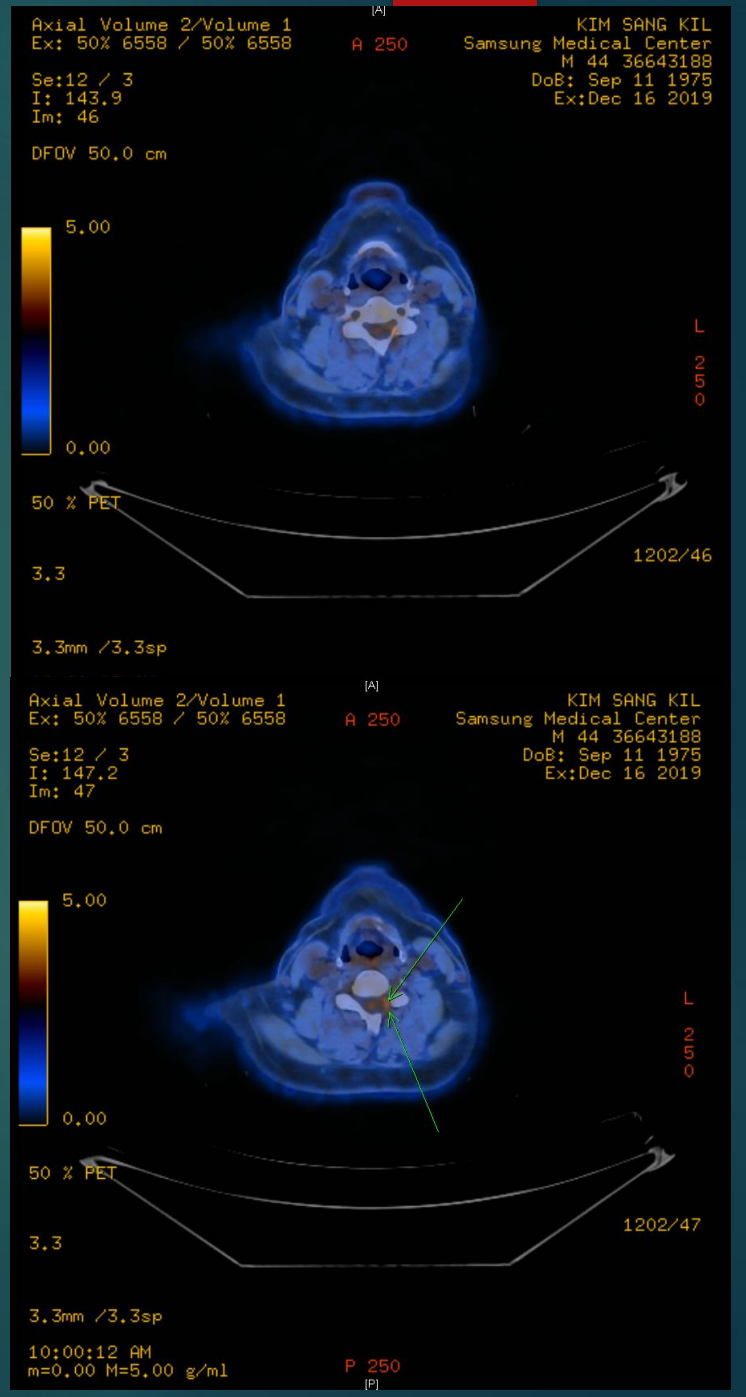




2019.12 C-spine MRI/PET

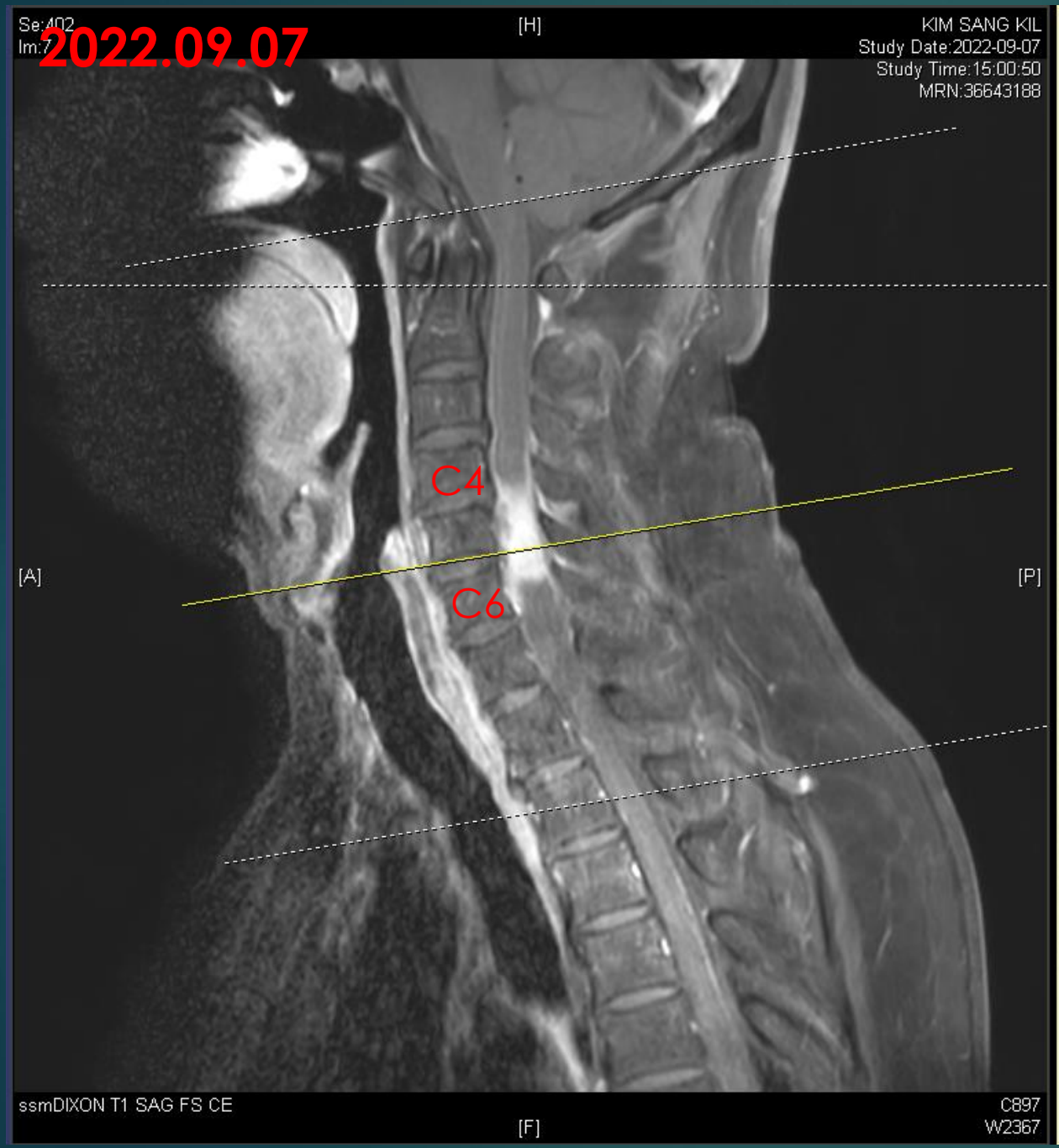






Recurred symptoms

- 2022.08.02 Lt forearm extensor side pain was reported.
- 2022.09.04 abrupt onset의 Lt upper extremity weakness 발생함.
- 2022.09.07 응급실 내원하여 C-spine MRI 촬영함.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C6
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C897
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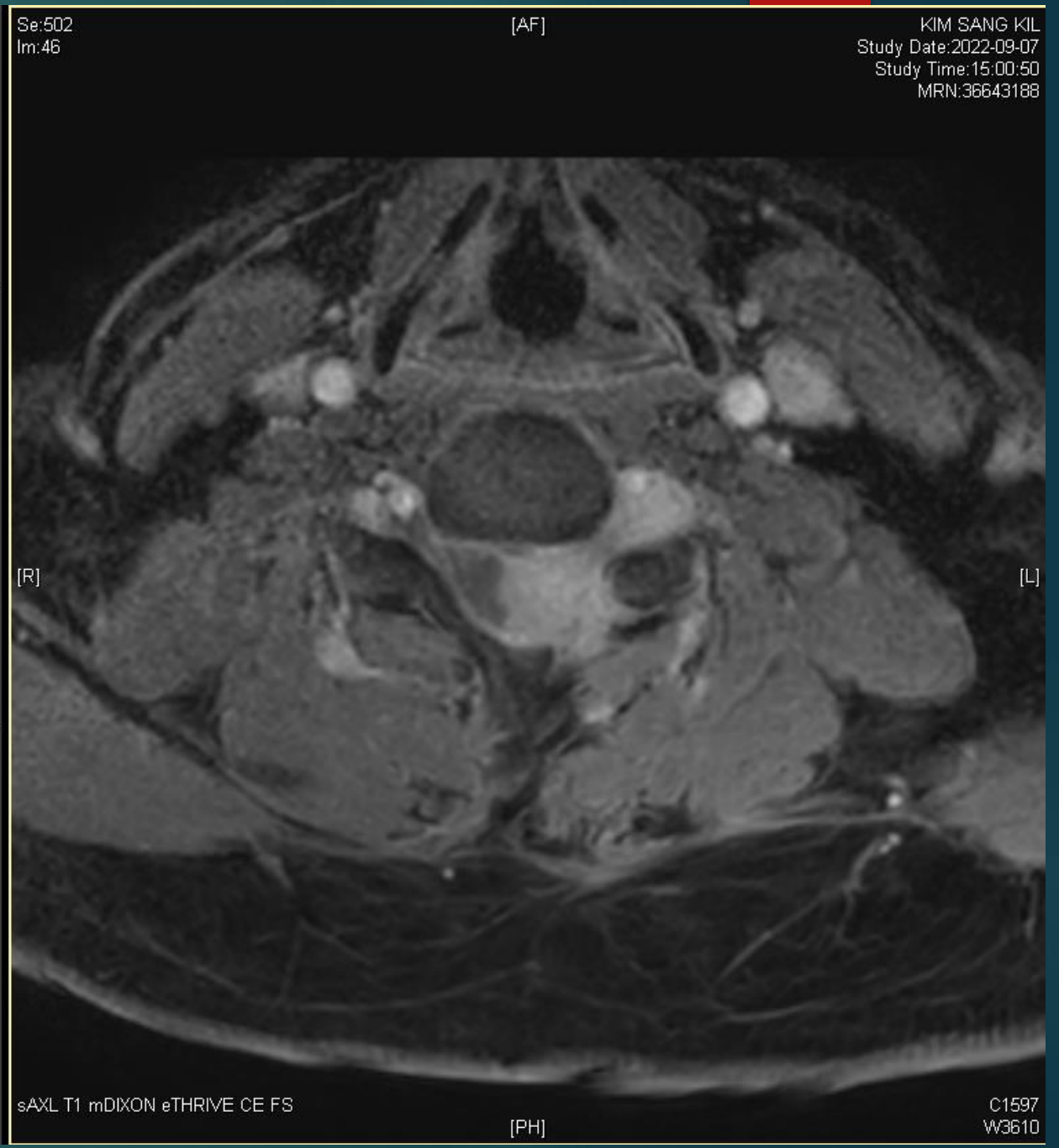
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C1597
W3610
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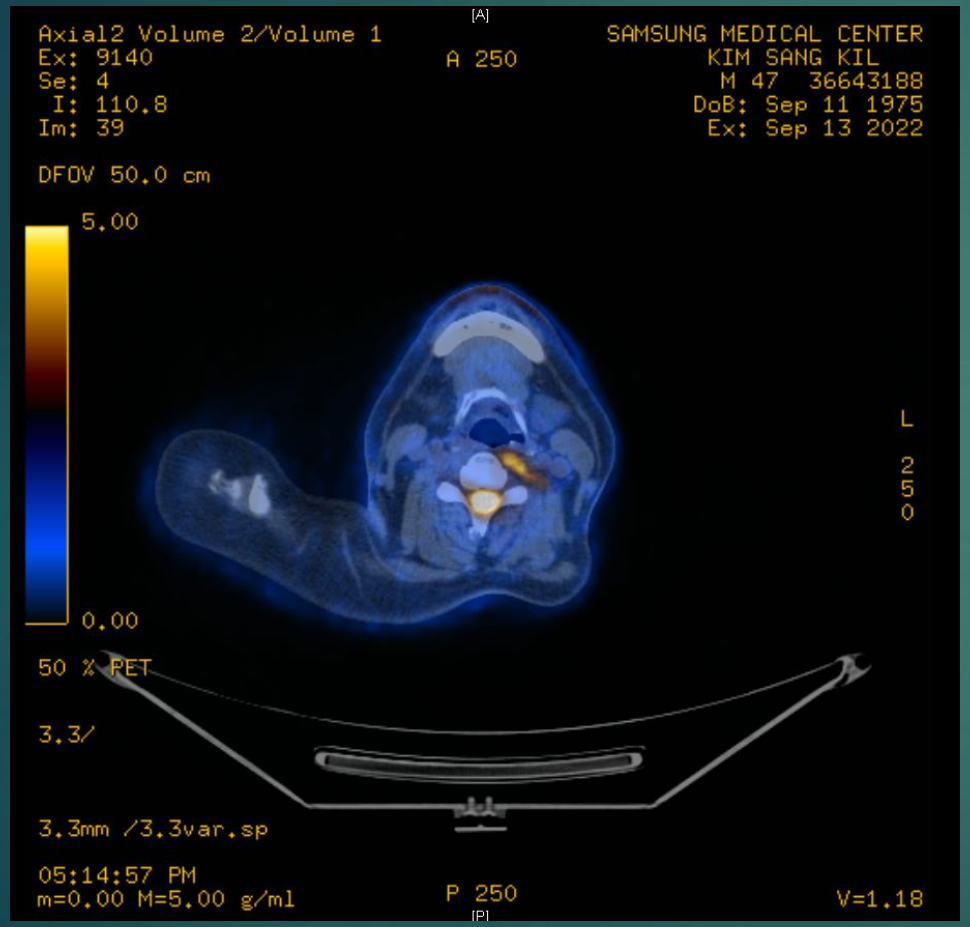
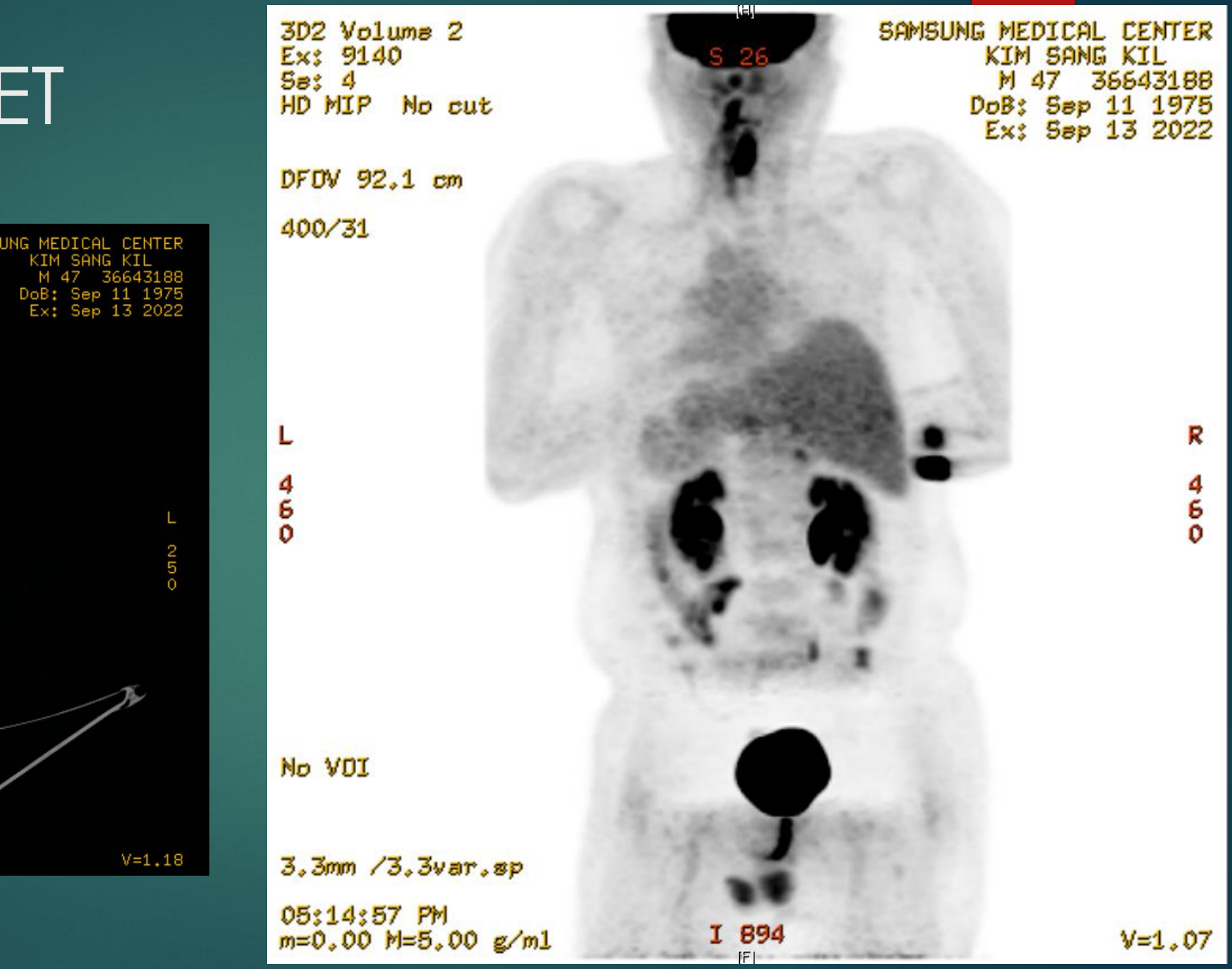
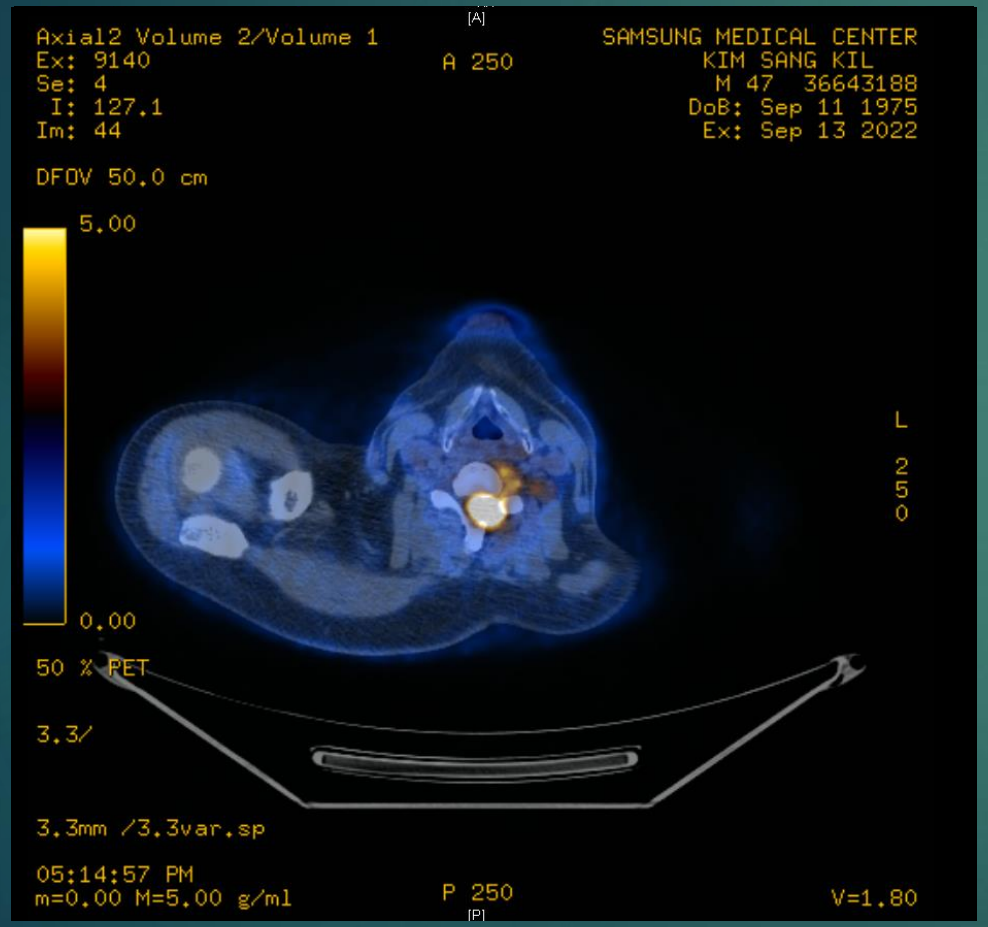
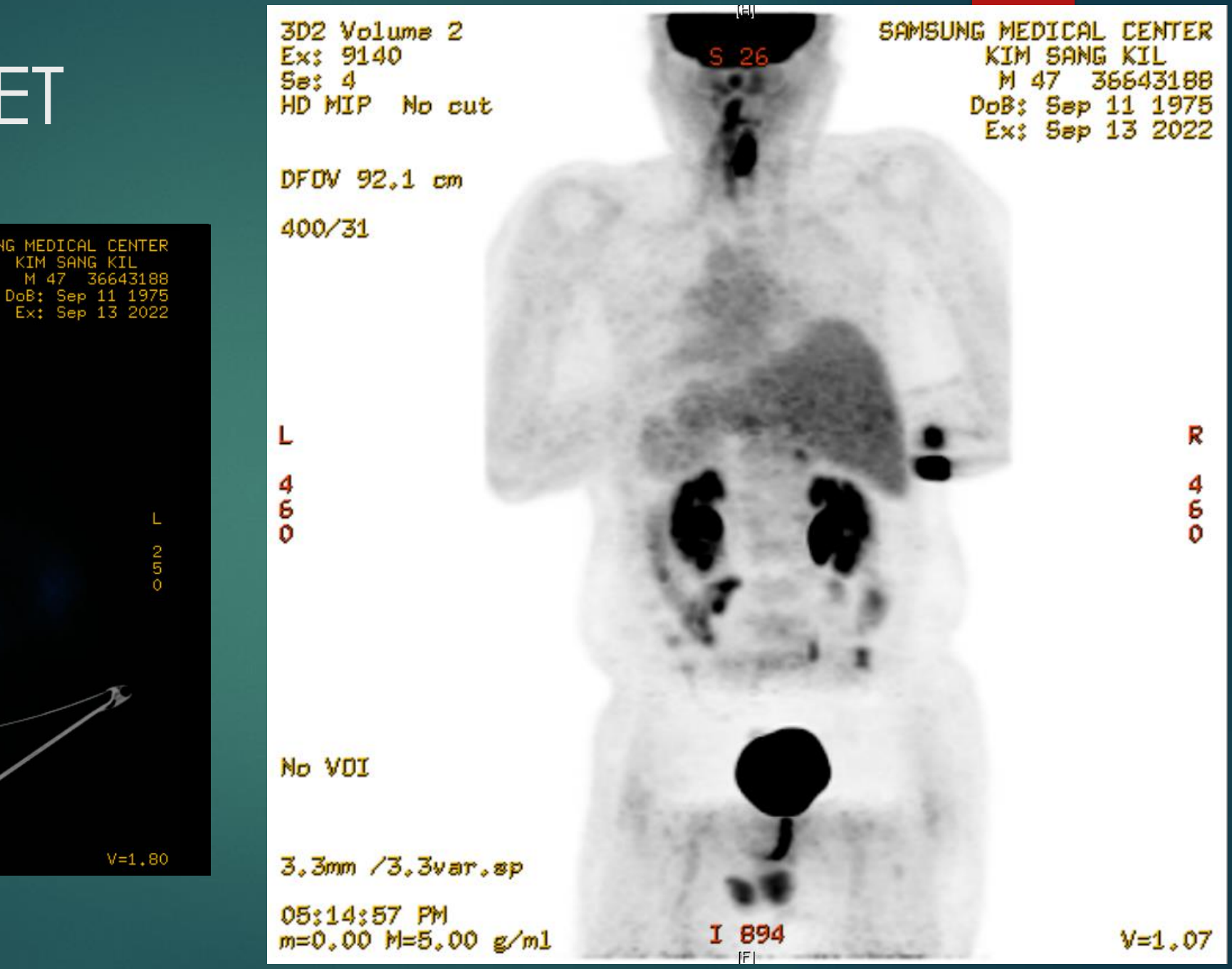
2022.09.13 PET





2022.09.13 PET





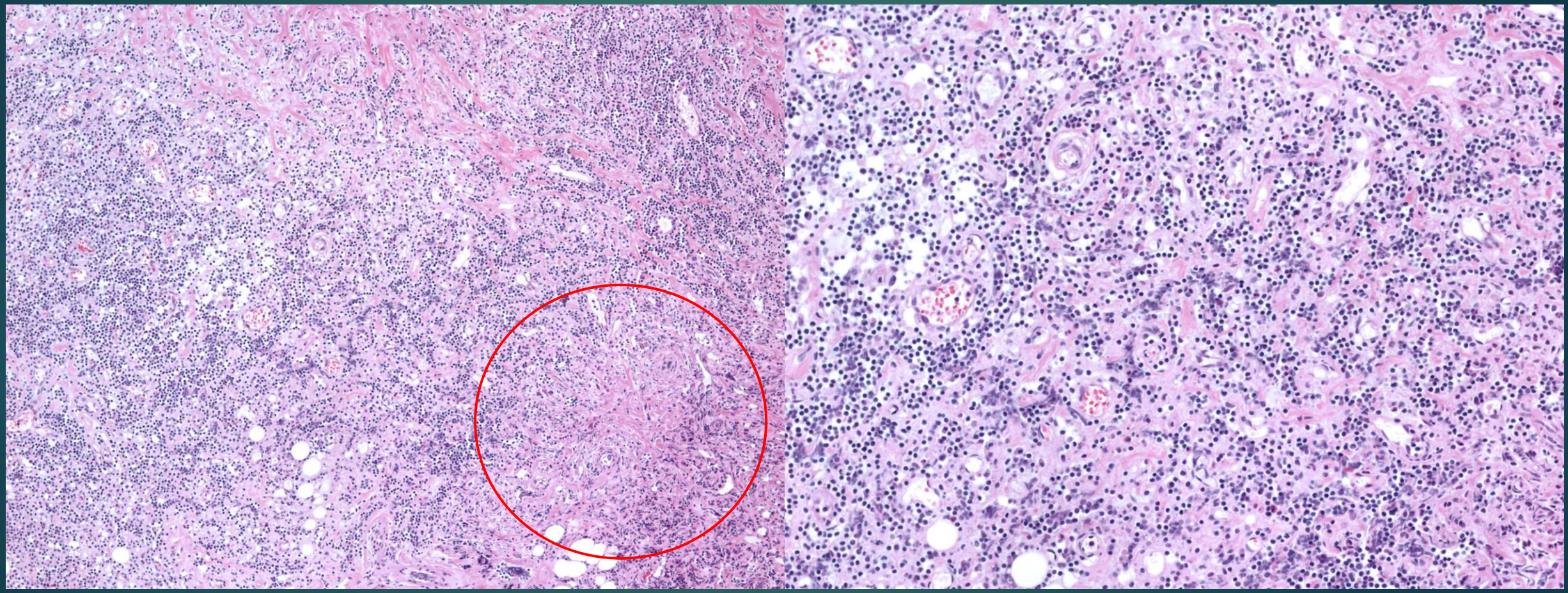
CSF analysis

- RBC: 7/uL
- WBC: 32/uL
- PMN: 8%
- Lymphocyte: 84%
- Neoplastic Cells: Negative
- ADA: 2.5 IU/L
- Glucose: 60 mg/dL (serum:
- **Protein: 55.3 mg/dL (WNL: 20~40)**

Hospital course

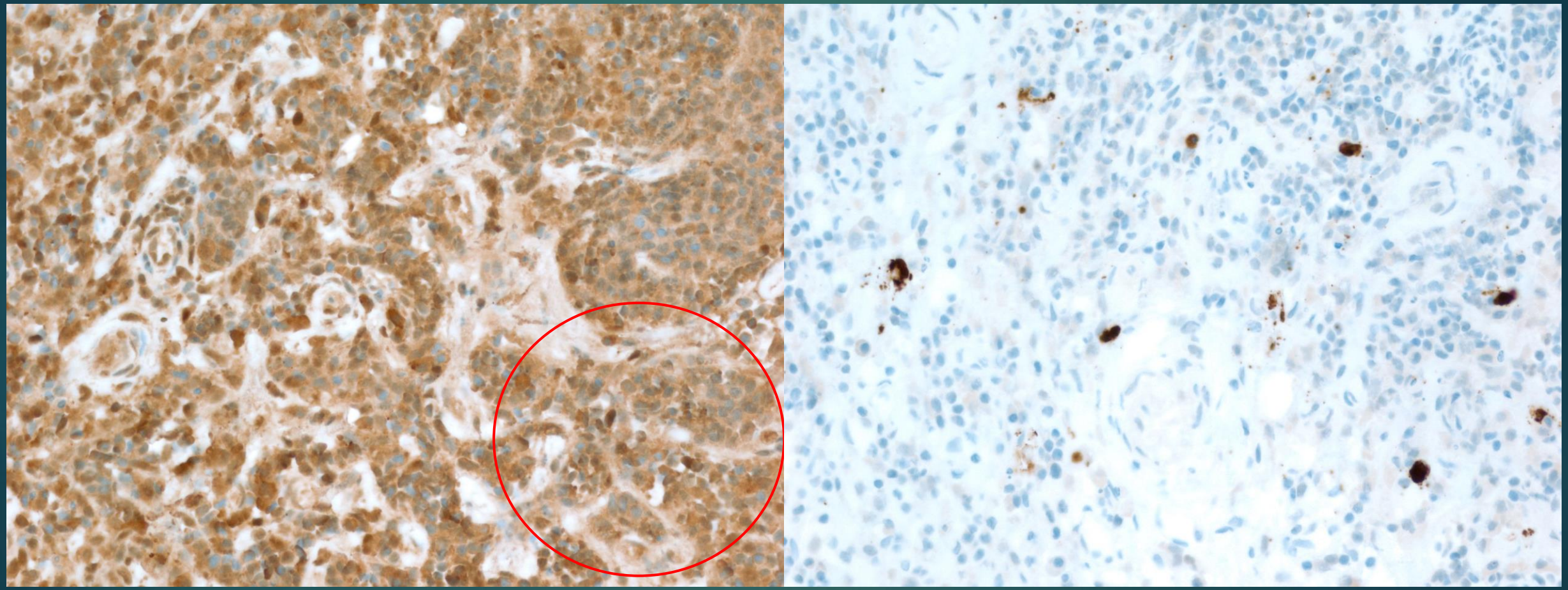
- 22.09.14 C4-5-6 open door laminoplasty c tumor removal

Biopsy of resected tumor



Dense infiltration by small inflammatory cells with storiform fibrosis

Biopsy of resected tumor



Left: IgG staining, Rt: IgG4 staining X400, less than 40%, more than 10 cells/HPF

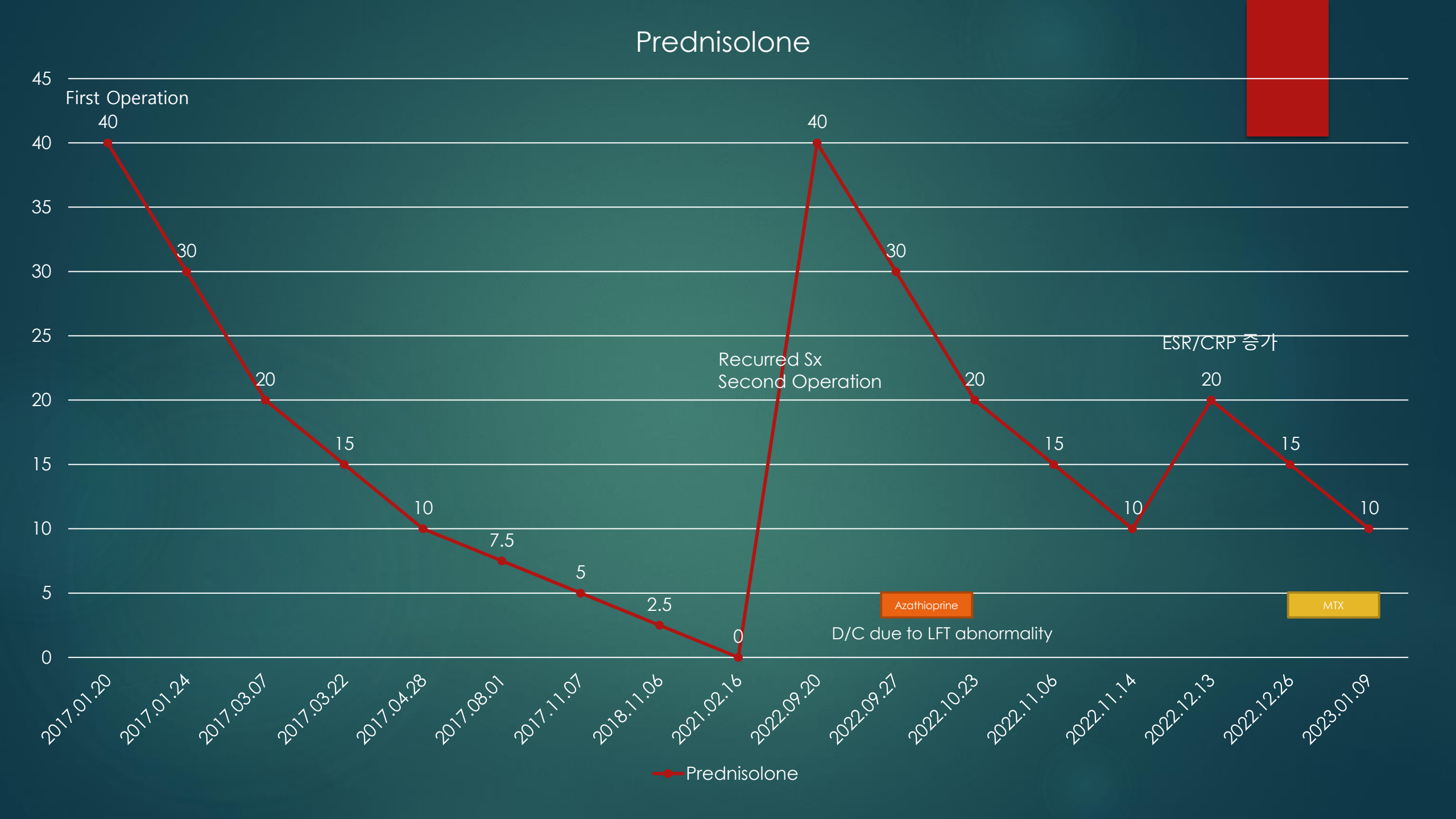
Comprehensive diagnostic criteria for IgG4-RD

- 1. Clinical or radiologic feature (+)
- 2. Serum IgG4 over 135mg/dl (-)
- 3. Histologic feature
  - **Dense lymphocyte and plasma cell infiltration with fibrosis (+)**
  - Ratio of IgG4-positive plasma cells / IgG-positive cells greater than 40% and the number of IgG4 positive plasma cell **greater than 10 per HPF (+)**
  - **Typical tissue fibrosis, particulary storiform fibrosis, or obliterative phlebitis.**

- 1+3으로 ***probable IgG4-RD***
- ***IgG4 Related pachymeningitis***

Final assessment

- IgG4 RD associated pachymeningitis


Prednisolone
45
40
35
30
25
20
15
10
5
0
First Operation
40
30
20
15
10
7.5
5
2.5
0
Recurred Sx
Second Operation
40
30
20
15
10
20
15
10
ESR/CRP 증가
Azathioprine
D/C due to LFT abnormality
MTX
2017.01.20
2017.01.24
2017.03.07
2017.03.22
2017.04.28
2017.08.01
2017.11.07
2018.11.06
2021.02.16
2022.09.20
2022.09.27
2022.10.23
2022.11.06
2022.11.14
2022.12.13
2022.12.26
2023.01.09
Prednisolone

IgG4 related disorder

DISEASE REVIEW

IgG4 related disorder

- Dr. Hideki Hamano first described in 2001 in 20 patients with sclerosing cholangitis.

Table 1. Age, Sex, and Serum Immunoglobulin Concentrations of Normal Subjects and Patients with Sclerosing Pancreatitis.*

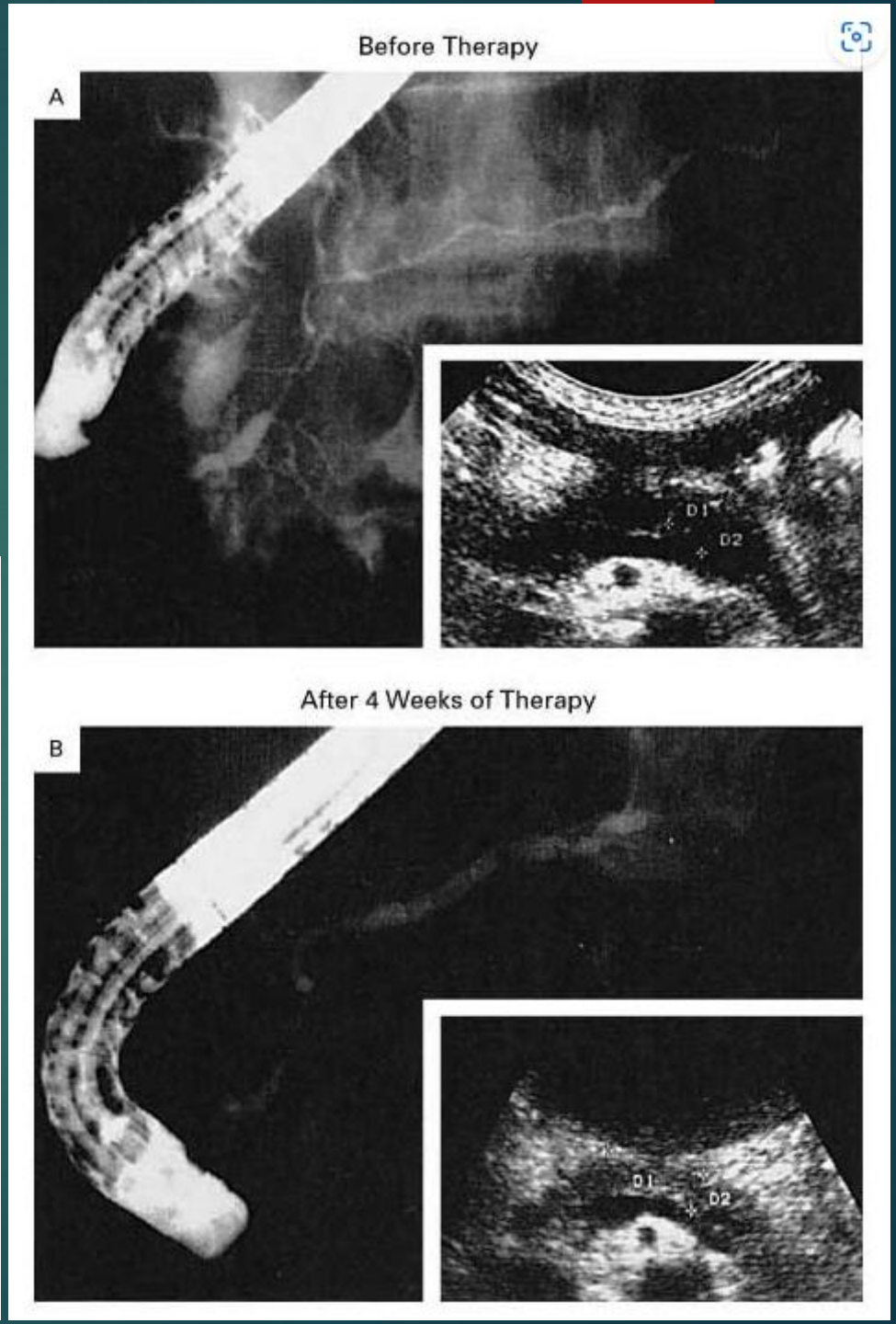
Characteristic	Normal Subjects (N=20)	Patients with Sclerosing Pancreatitis (N=20)	P Value†
Age — yr	61±11	61±11	1.00
Male sex — no. (%)	15 (75)	15 (75)	1.00
	median (5th, 95th percentiles)		
Serum IgG1 — mg/dl			
Single radial immunodiffusion	664 (498, 1036)	868 (401, 1784)	0.25
ELISA	859 (698, 1077)	1095 (464, 1991)	0.03
Serum IgG2 — mg/dl			
Single radial immunodiffusion	592 (403, 902)	617 (330, 1234)	0.99
ELISA	510 (326, 726)	366 (263, 639)	0.03
Serum IgG3 — mg/dl			
Single radial immunodiffusion	34 (3, 100)	53 (13, 174)	0.12
ELISA	38 (11, 76)	51 (17, 101)	0.38
Serum IgG4 — mg/dl			
Single radial immunodiffusion	51 (15, 128)	663 (136, 1150)	<0.001
ELISA	41 (14, 156)	597 (24, 1230)	<0.001
Serum IgA — mg/dl‡	247 (144, 392)	226 (85, 552)	0.44
Serum IgM — mg/dl‡	142 (73, 221)	91 (40, 236)	0.11
Serum IgE — IU/ml§	79 (10, 240)	176 (62, 405)	0.09

*Plus–minus values are means ±SD. ELISA denotes enzyme-linked immunosorbent assay.

†The Mann–Whitney test was used to calculate two-sided P values.

‡A turbidimetric immunoassay was used to measure serum IgA and IgM concentrations.

§An enzyme-linked immunosorbent assay was used to measure serum IgE concentrations. To convert values to micrograms per liter, multiply by 2.4.

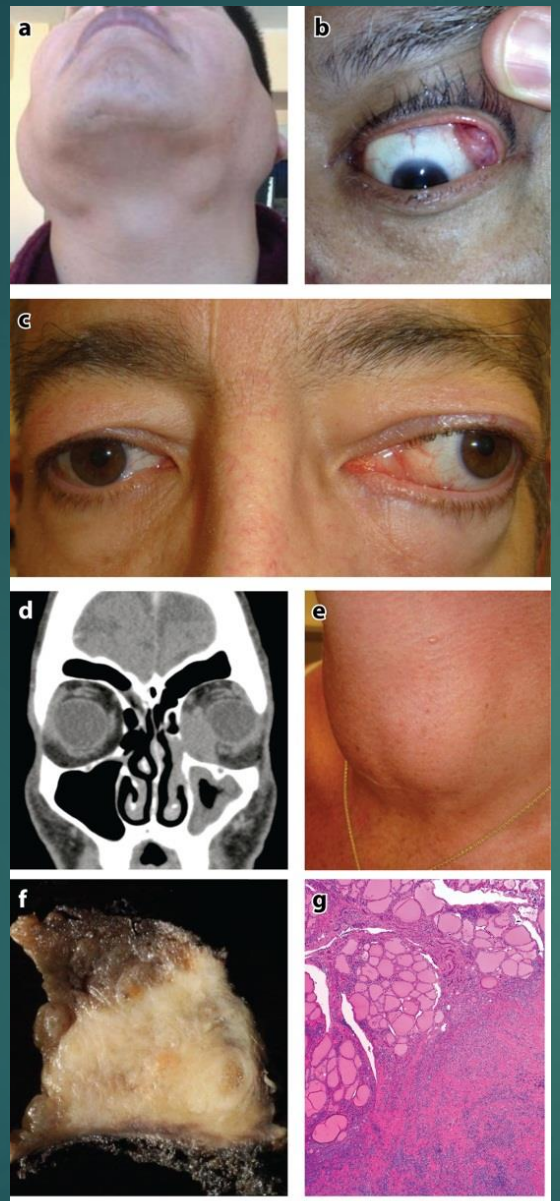


Epidemiology

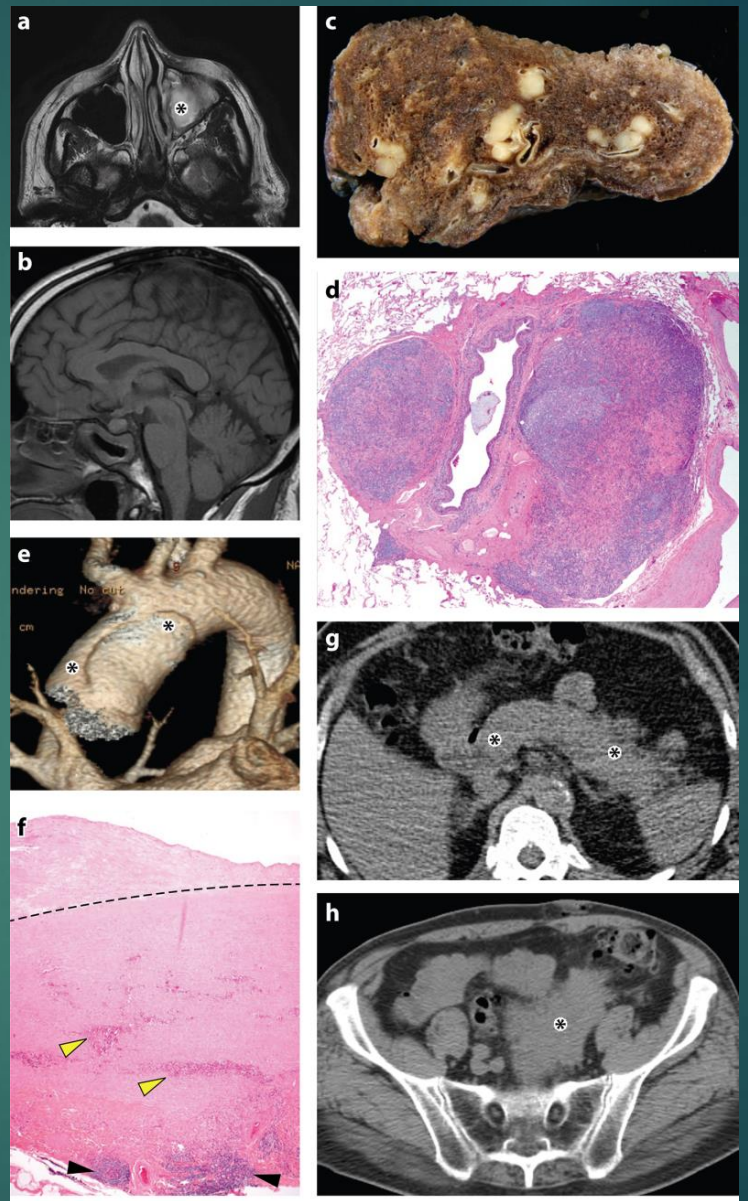
- Typical patents; middle aged to elderly man
- Assumed very rare.
- Poorly described due to recent recognition.

Clinical Symptoms

- Dependent on the affected organ
  - Autoimmune pancreatitis
  - Lung, thyroid
  - Lacrimal and salivary gland
  - CNS involvement
  - Organ swelling and compression symptoms.
  - Could be misdiagnosed as tumorous conditions



Mahajan VS, et al. 2014.
Annu. Rev. Pathol. Mech. Dis. 9:315–47

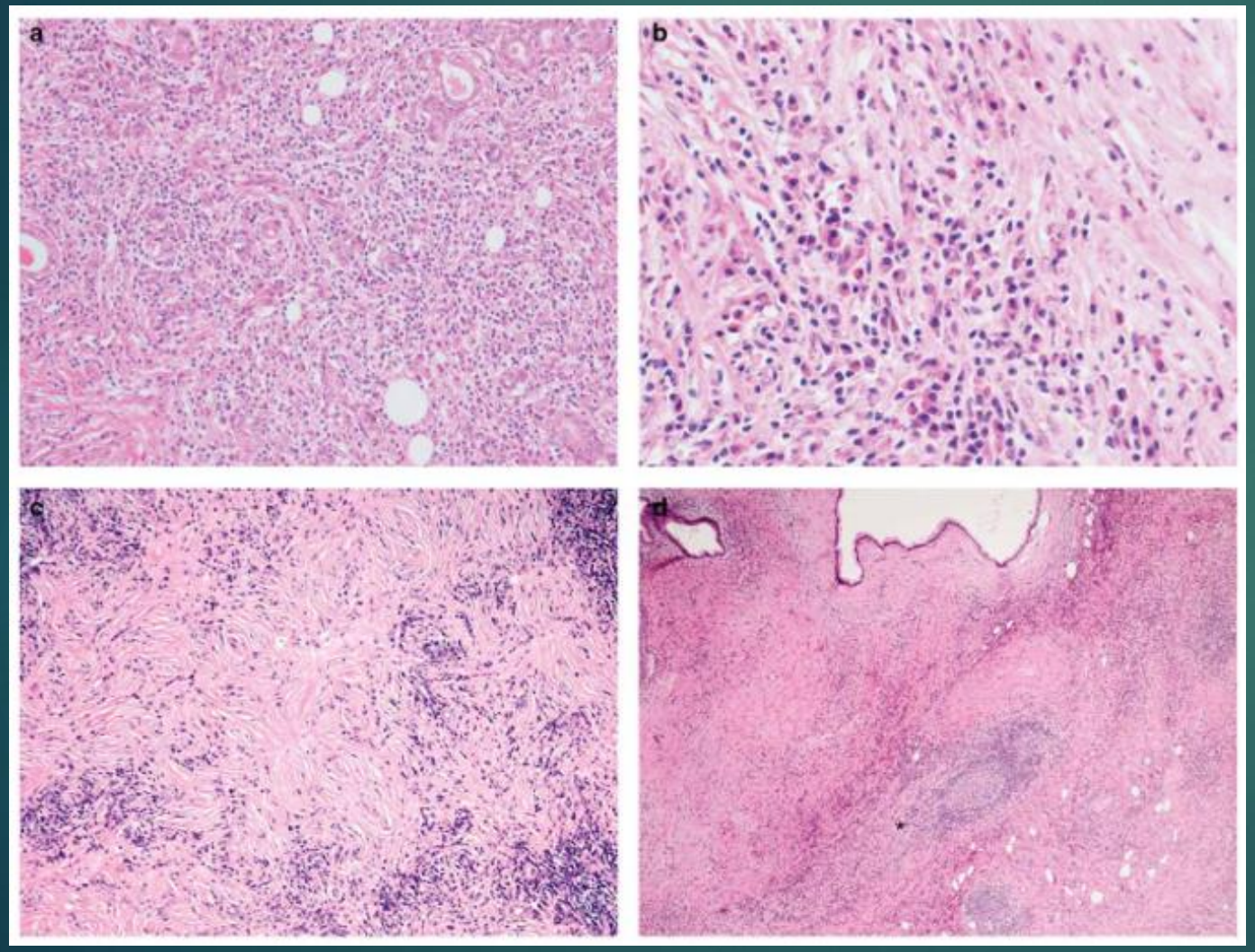


Mahajan VS, et al. 2014.
Annu. Rev. Pathol. Mech. Dis. 9:315–47

Diagnosis

- In early days, diagnosis is dependent on the incidental pathological findings of lesions with suspected malignancy.
- Lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis, and dramatic IgG4+ plasma cell infiltrate.

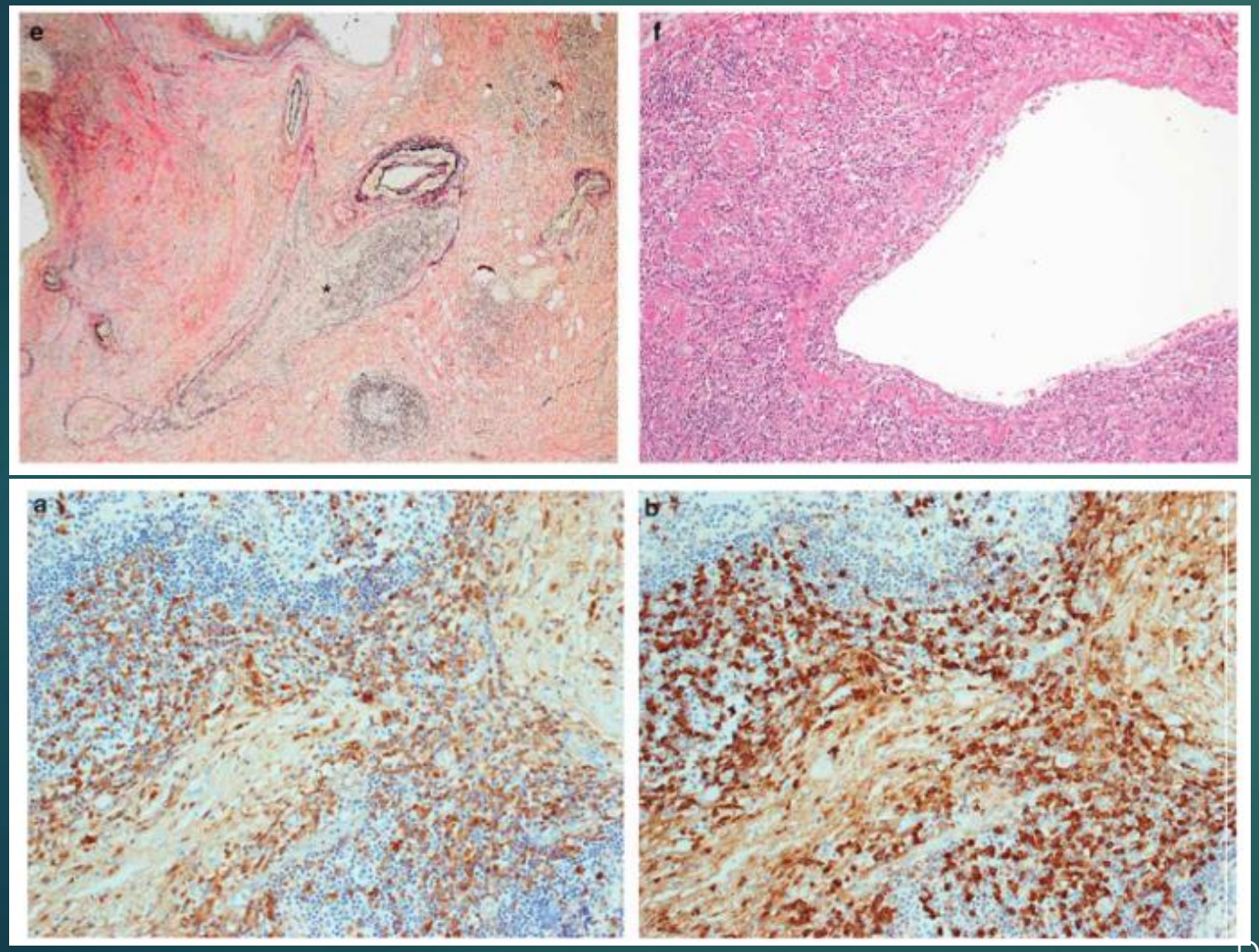
Pathology of affected organ



a) IgG4-related sialadenitis. The salivary gland is extensively **infiltrated by inflammatory cells**, which consist of lymphocytes and plasma cells.
b) IgG4-related sialadenitis. A moderate number of eosinophils are present. H&E, 400.
c) IgG4-related orbital disease. IgG4-related disease typically shows an irregularly whorled pattern of fibrosis (**storiform fibrosis**).
d) Type 1 autoimmune pancreatitis (IgG4-related pancreatitis). The vein (*) is completely obliterated byaggregated inflammatory cell infiltration **(obliterative phlebitis).**

Deshpande et al, Modern Pathology (2012) 25, 1181–1192

Pathology of affected organ



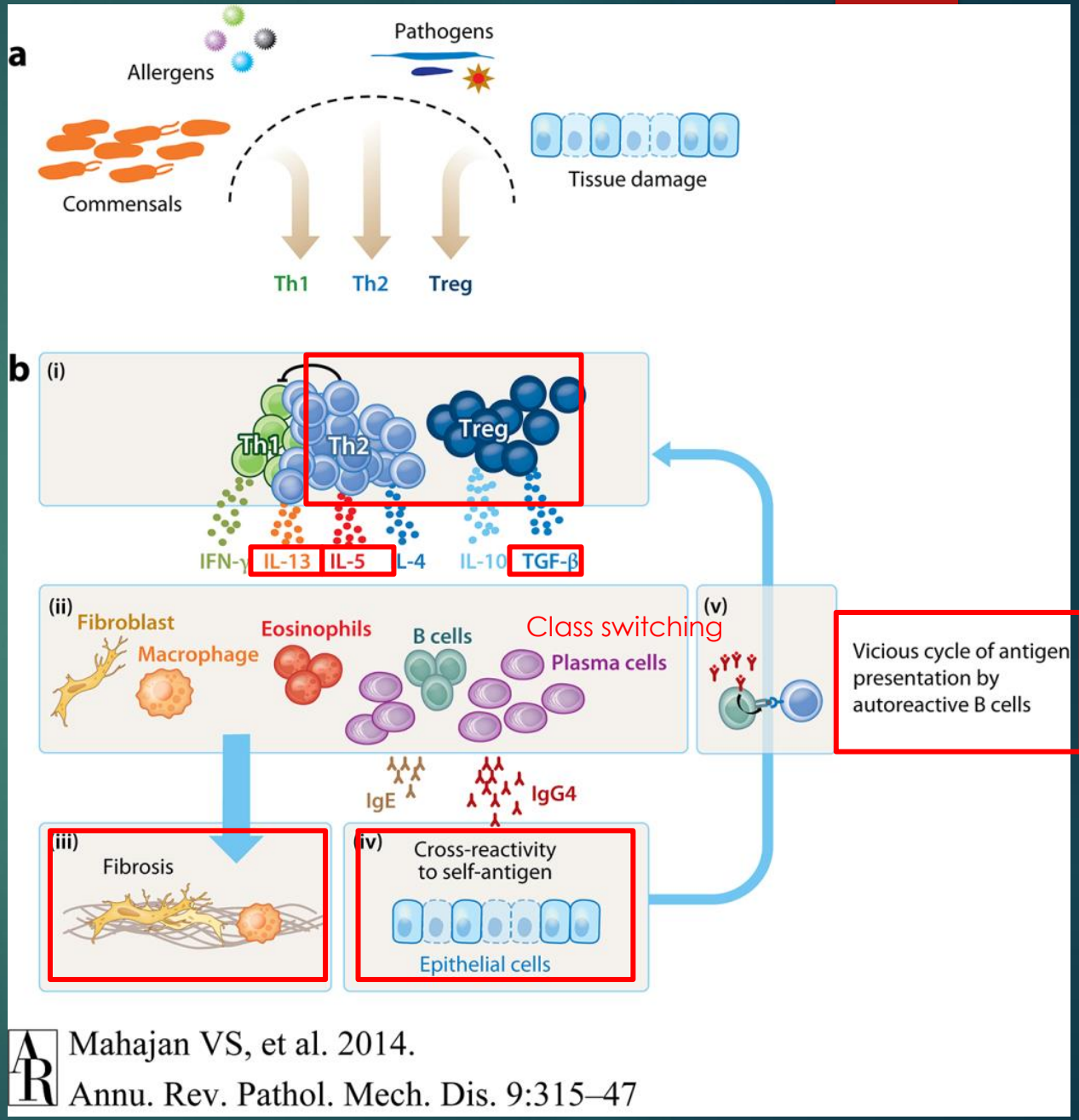
e. obliterated vein is only seen on the elastin stain, 100.

f. Type 1autoimmune pancreatitis (IgG4-related pancreatitis). The vein shows transmural infiltration by inflammatory cells, but is not associated with luminal obliteration.

Immunostaining for IgG and IgG4 in IgG4-related dacryoadenitis. The majority of IgG-positive plasma cells (a) appear positive for IgG4 (b). (a) IgG immunostaining and (b) IgG4 immunostaining, both at x200.

Deshpande et al, Modern Pathology (2012) 25, 1181–1192

Pathophysiology

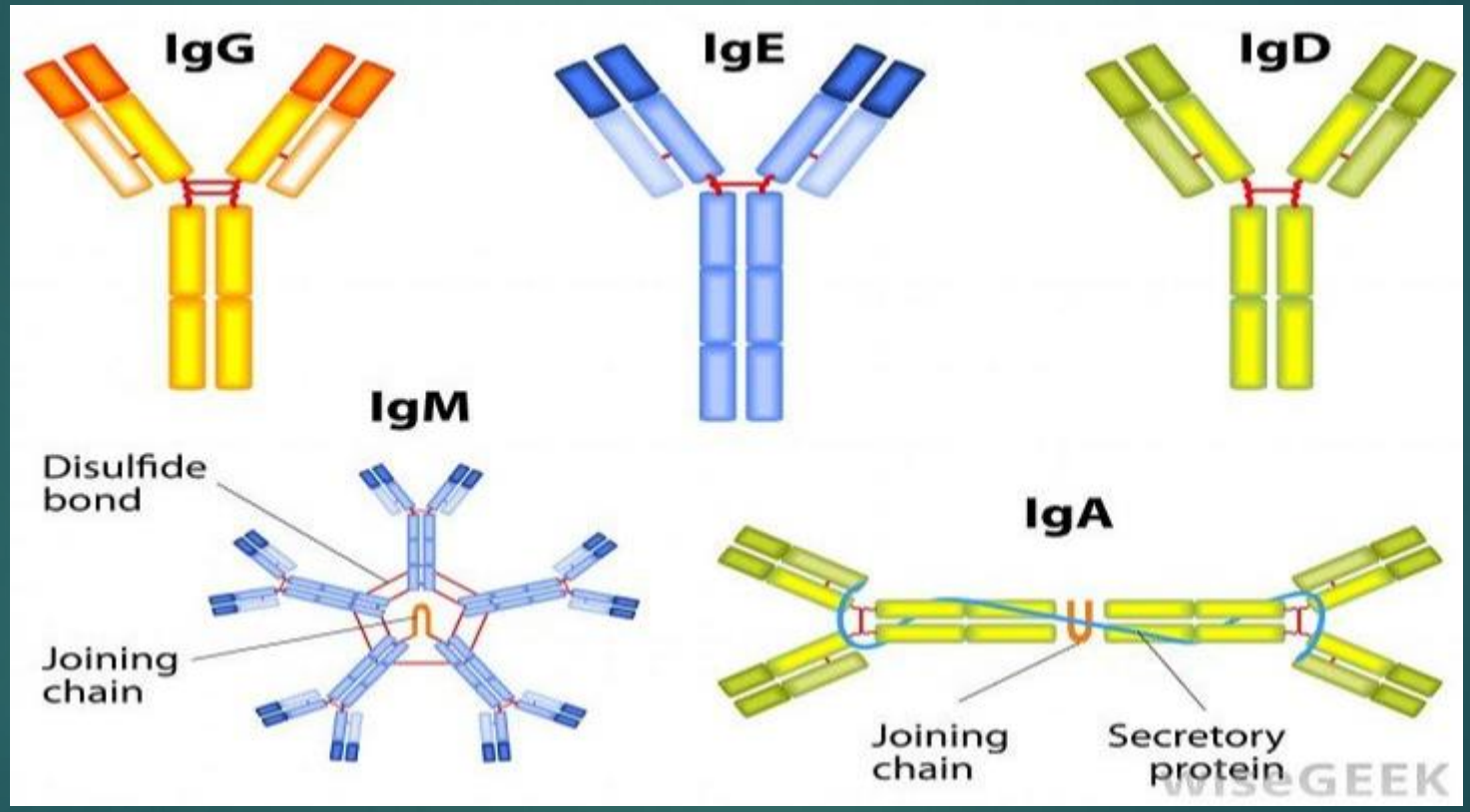


Mahajan VS, et al. 2014.
Annu. Rev. Pathol. Mech. Dis. 9:315–47

Pathophysiology of IgG4 RD

- What is igG4 subtype?
- Antibody class switching in plasma cells
- What are the triggering factors to generate a certain isotype?

Antibody Subtypes



IgG4 class subtype

Weak disulfide bonding between heavy chain

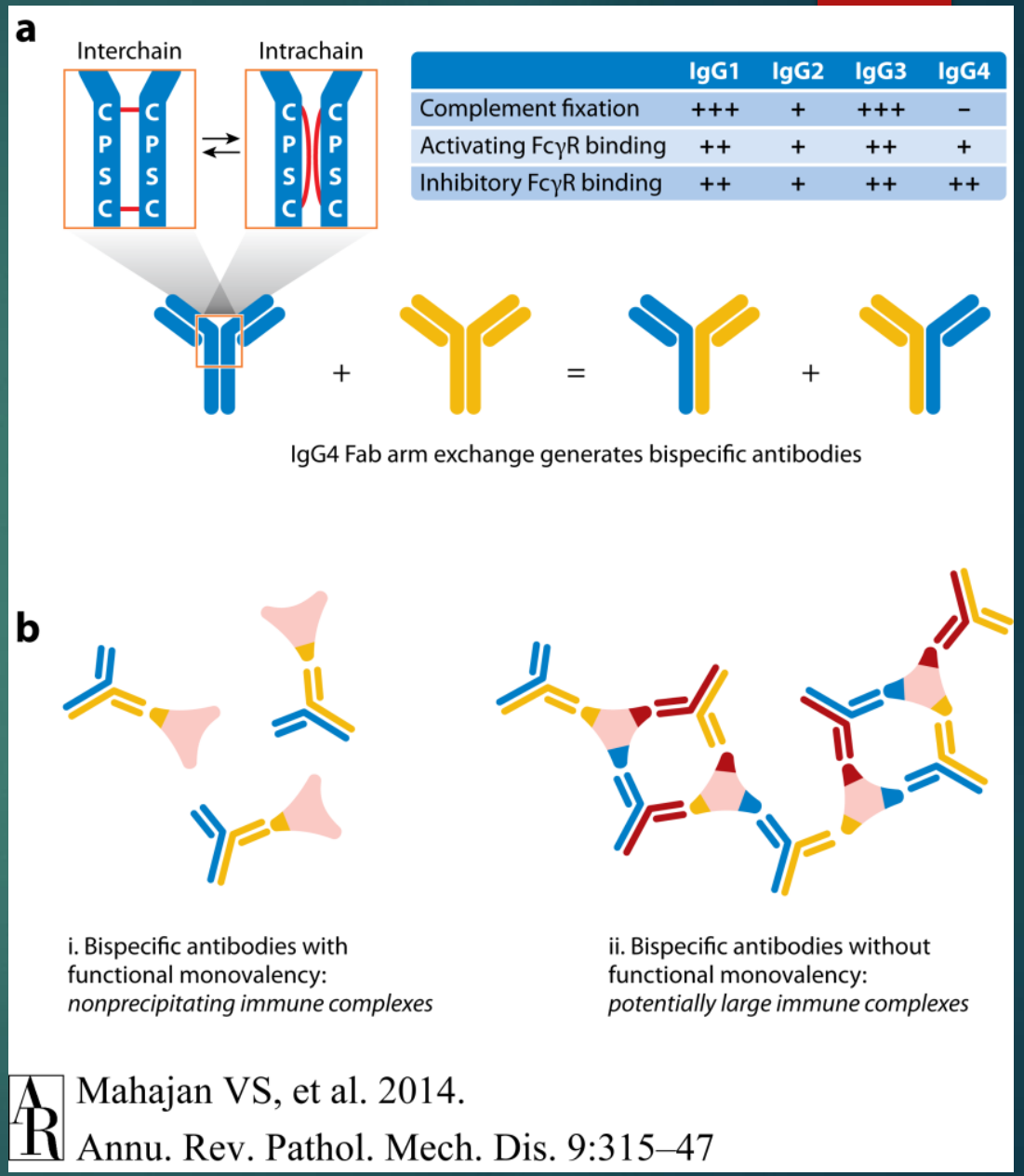
Fab arm exchange

Low affinity and activating ability of complement

Known as inhibitory immunoglobulin

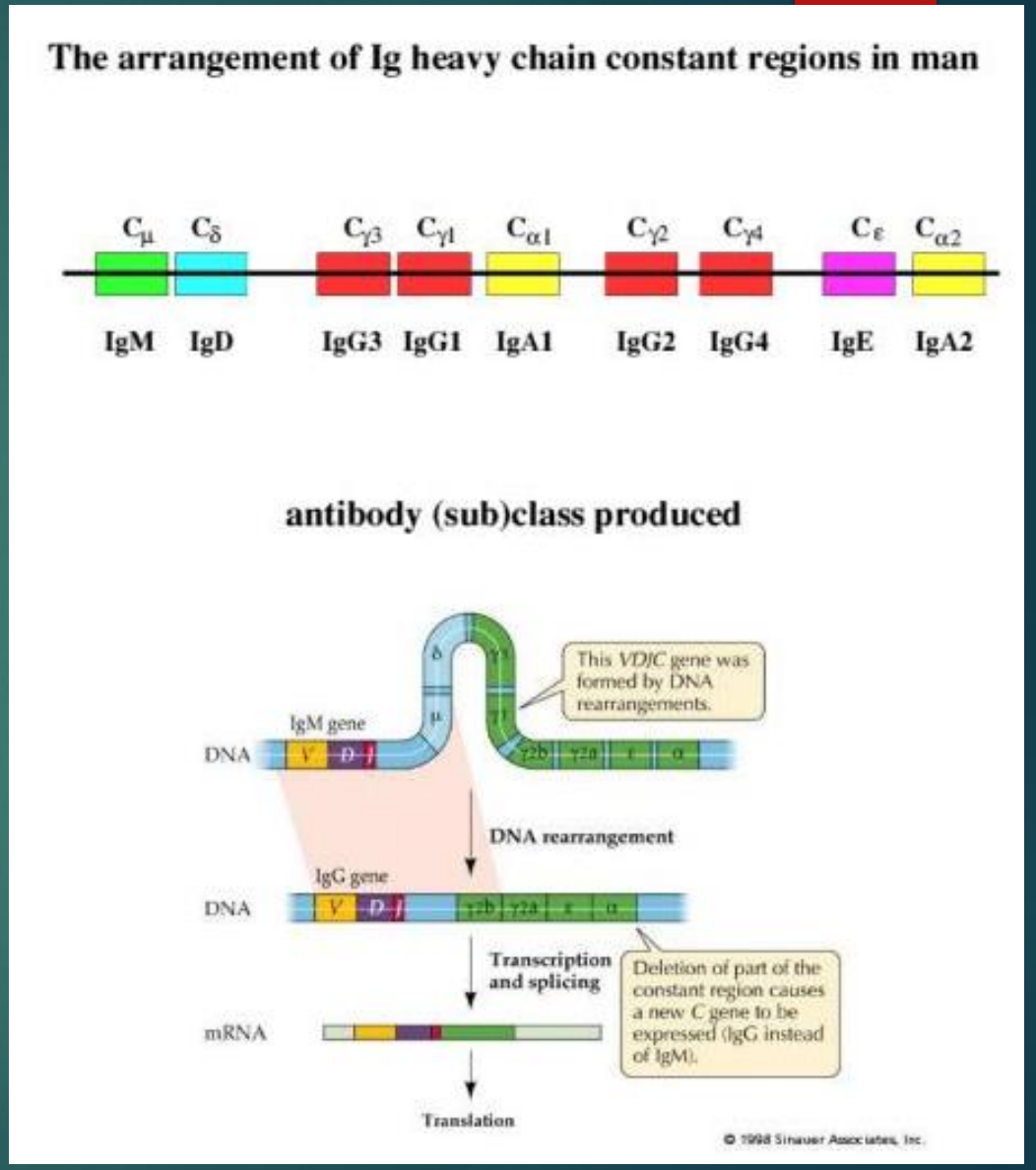
Bispecific antibodies could potentiate the

Large immune complexes not easily eradicated.

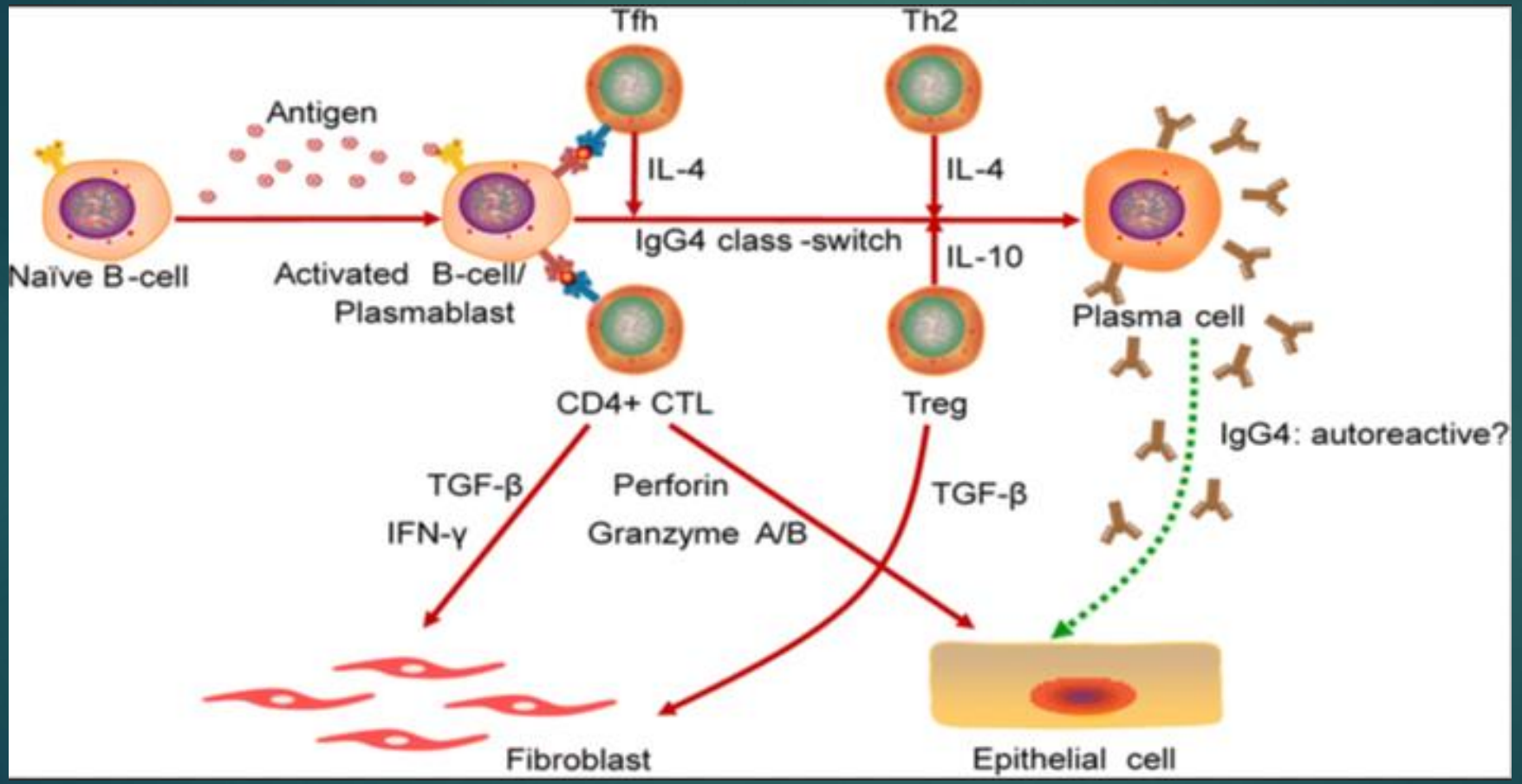


Class switching

- Naïve B-cell; only mIgM, mIgD
- Plasma cell; produces several isotype of immunoglobulin after class switching
- Class switching; irreversible phenomenon



Cytokines are key elements



IL-4: IgG4 class switching

Chronic inflammation

IL-10:

IgG4 upregulation

IgE down regulation

TGF-b: Fibrosis

Pathophysiology

- Potential external stimuli? : Unknown
- Genetic trait? : Might be.
  - Unknown
- Chronic inflammation and class switching to IgG4

Diagnosis

- 2011 Comprehensive diagnostic criteria for IgG4-RD
- 2019 ACR/EULAR classification criteria
- 2020 Revised comprehensive diagnostic criteria for IgG4-RD

2019 ACR/EULAR classification criteria

Step 1. Entry criteria	**Yes**† or No
Characteristic* clinical or radiologic involvement of a typical organ (e.g., pancreas, salivary glands, bile ducts, orbits, kidney, lung, aorta, retroperitoneum, pachymeninges, or thyroid gland [Riedel's thyroiditis]) OR pathologic evidence of an inflammatory process accompanied by a lymphoplasmacytic infiltrate of uncertain etiology in one of these same organs	

Step 2. Exclusion criteria: domains and items‡	Yes or **No**§
Clinical	
Fever	
No objective response to glucocorticoids	
Serologic	
Leukopenia and thrombocytopenia with no explanation	
Peripheral eosinophilia	
Positive antineutrophil cytoplasmic antibody (specifically against proteinase 3 or myeloperoxidase)	
Positive SSA/Ro or SSB/La antibody	
Positive double-stranded DNA, RNP, or Sm antibody	
Other disease-specific autoantibody	
Cryoglobulinemia	
Radiologic	
Known radiologic findings suspicious for malignancy or infection that have not been sufficiently investigated	
Rapid radiologic progression	
Long bone abnormalities consistent with Erdheim-Chester disease	
Splenomegaly	
Pathologic	
Cellular infiltrates suggesting malignancy that have not been sufficiently evaluated	
Markers consistent with inflammatory myofibroblastic tumor	
Prominent neutrophilic inflammation	
Necrotizing vasculitis	
Prominent necrosis	
Primarily granulomatous inflammation	
Pathologic features of macrophage/histiocytic disorder	
Known diagnosis of the following:	
Multicentric Castleman's disease	
Crohn's disease or ulcerative colitis (if only pancreatobiliary disease is present)	
Hashimoto thyroiditis (if only the thyroid is affected)	

If case meets entry criteria and does not meet any exclusion criteria, proceed to step 3.

Step 3. Inclusion criteria: domains and items¶

Histopathology	
Uninformative biopsy	0
Dense lymphocytic infiltrate	+4
Dense lymphocytic infiltrate and obliterative phlebitis	+6
Dense lymphocytic infiltrate and storiform fibrosis with or without obliterative phlebitis	+13
Immunostaining#	0–16, as follows:

Assigned weight is 0 if the IgG4+:IgG+ ratio is 0–40% or indeterminate and the number of IgG4+ cells/hpf is 0–9.**

Assigned weight is 7 if 1) the IgG4+:IgG+ ratio is ≥41% and the number of IgG4+ cells/hpf is 0–9 or indeterminate; or 2) the IgG4+:IgG+ ratio is 0–40% or indeterminate and the number of IgG4+ cells/hpf is ≥10 or indeterminate.

Assigned weight is 14 if 1) the IgG4+:IgG+ ratio is 41–70% and the number of IgG4+ cells/hpf is ≥10; or 2) the IgG4+:IgG+ ratio is ≥71% and the number of IgG4+ cells/hpf is 10–50.

Assigned weight is 16 if the IgG4+:IgG+ ratio is ≥71% and the number of IgG4+ cells/hpf is ≥51.

13+7

(Continued)

Serum IgG4 concentration	
Normal or not checked	0
> Normal but <2× upper limit of normal	+4
2–5× upper limit of normal	+6
>5× upper limit of normal	+11
Bilateral lacrimal, parotid, sublingual, and submandibular glands	
No set of glands involved	0
One set of glands involved	+6
Two or more sets of glands involved	+14
Chest	
Not checked or neither of the items listed is present	0
Peribronchovascular and septal thickening	+4
Paravertebral band-like soft tissue in the thorax	+10
Pancreas and biliary tree	
Not checked or none of the items listed is present	0
Diffuse pancreas enlargement (loss of lobulations)	+8
Diffuse pancreas enlargement and capsule-like rim with decreased enhancement	+11
Pancreas (either of above) and biliary tree involvement	+19
Kidney	
Not checked or none of the items listed is present	0
Hypocomplementemia	+6
Renal pelvis thickening/soft tissue	+8
Bilateral renal cortex low-density areas	+10
Retroperitoneum	
Not checked or neither of the items listed is present	0
Diffuse thickening of the abdominal aortic wall	+4
Circumferential or anterolateral soft tissue around the infrarenal aorta or iliac arteries	+8

2019 ACR/EULAR classification criteria

Step 4: Total inclusion points

A case meets the classification criteria for IgG4-RD if the entry criteria are met, no exclusion criteria are present, and the total points is ≥20.

Table 5. Performance of various thresholds of the 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease using validation cohort 1*

Threshold	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Youden index	Distance to (0,1)	Specificity − sensitivity	Diagnostic odds ratio
14	0.89 (0.86–0.92)	0.95 (0.91–0.97)	0.92 (0.90–0.94)	0.84	0.12	0.06	142.4
15	0.89 (0.85–0.91)	0.97 (0.95–0.99)	0.93 (0.91–0.95)	0.86	0.12	0.09	286.1
16	0.89 (0.85–0.91)	0.98 (0.96–0.99)	0.93 (0.92–0.95)	0.87	0.12	0.10	394.5
17	0.88 (0.85–0.91)	0.98 (0.96–0.99)	0.93 (0.92–0.95)	0.86	0.12	0.10	385.6
18	0.88 (0.84–0.90)	0.98 (0.96–0.99)	0.93 (0.91–0.95)	0.86	0.13	0.11	360.8
19	0.86 (0.83–0.89)	0.99 (0.92–0.99)	0.93 (0.91–0.94)	0.85	0.14	0.12	408.3
20	0.86 (0.82–0.89)	0.99 (0.97–100.0)	0.92 (0.91–0.94)	0.85	0.15	0.14	761.5
21	0.83 (0.79–0.86)	0.99 (0.97–0.99)	0.91 (0.89–0.93)	0.82	0.18	0.17	607.2
22	0.82 (0.78–0.85)	0.99 (0.97–0.99)	0.91 (0.89–0.92)	0.81	0.18	0.18	578.8

* 95% CI = 95% confidence interval; AUC = area under the curve.

Comprehensive diagnostic criteria for IgG4-RD

(1) Clinical examination shows characteristic diffuse/localized swelling or masses in single or multiple organs

(2) Elevated serum IgG4 concentrations (≧135 mg/dL)

(3) Histopathologic examination shows:

A. Marked lymphocyte and plasmacyte infiltration and fibrosis

B. Infiltration of IgG4+ plasma cells: ratio of IgG4+/IgG+cells ≧40 % and ≧10 IgG4+ plasma cells per high power field

Definite	IgG-RD:	(1) + (2) + (3)
Probable	IgG4-RD:	(1) + (3)
Possible	IgG4-RD:	(1) + (2)

It is important to differentiate IgG4-RD from malignant tumors of each organ (e.g., cancer, lymphoma) and from similar diseases (e.g., Sjögren's syndrome, primary sclerosing cholangitis, Castleman disease, secondary retroperitoneal fibrosis, Wegener granulomatosis, sarcoidosis, Churg-Strauss syndrome). Even when patients cannot be diagnosed using the criteria, they may be diagnosed using the organ-specific diagnostic criteria for IgG4-RD

2011 classification criteria

Table 2. The 2020 Revised comprehensive diagnostic (RCD) criteria for IgG4-RD.

[Item 1] clinical and radiological features
One or more organs show diffuse or localized swelling or a mass or nodule characteristic of IgG4-RD. In single organ involvement, lymph node swelling is omitted.
[Item 2] serological diagnosis
Serum IgG4 levels greater than 135 mg/dl.
[Item 3] pathological diagnosis
Positivity for two of the following three criteria:
① Dense lymphocyte and plasma cell infiltration with fibrosis.
② Ratio of IgG4-positive plasma cells /IgG-positive cells greater than 40% and the number of IgG4-positive plasma cells greater than 10 per high powered field
③Typical tissue fibrosis, particularly storiform fibrosis, or obliterative phlebitis
Diagnosis:
Definite: 1) +2) +3)
Probable: 1) +3):
Possible: 1) +2)

Explanatory note 1: Combination of organ-specific diagnostic criteria*.
Patients with a possible or probable diagnosis by comprehensive diagnostic criteria who fulfill the organ-specific criteria for IgG4-RD are regarded as being definite for IgG4-RD.
*Diagnostic criteria according to the IgG4-related organ:.
① International consensus diagnostic criteria for autoimmune pancreatitis[7], ② IgG4-related lacrimal gland, saliva adenitis diagnostic criteria[8], ③ Diagnostic criteria for IgG4-related kidney disease[9], ④ Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012[10], ⑤Diagnostic criteria for IgG4-related ophthalmic disease[11], ⑥Diagnostic criteria for IgG4-related respiratory disease[12], ⑦ Diagnostic criteria for IgG4-related large periarteritis/periarteritis and retroperitoneal fibrosis[13].
Explanatory note 2: exclusion diagnosis.
1) It is important to acquire tissue samples from each involved organ to distinguish malignant tumors (e.g. cancer, malignant lymphoma) and similar benign conditions (e.g. Sjögren syndrome, primary sclerosing cholangitis, multicentric Castleman's disease, secondary retroperitoneal fibrosis, granulomatosis with polyangiitis, sarcoidosis, eosinophilic granulomatosis with polyangiitis).
2) It is important to exclude an infectious- or inflammation-related disease in patients with high fever, highly elevated CRP and neutrophilia.
Explanatory note 3: pathologic diagnosis.
1) The numbers of IgG4-positive cells are usually more abundant in resected organs and partially enucleated tissue than in tissue samples obtained by needle biopsy or endoscopic biopsy. Thus, it is important to not be too particular about cell number and to provide a precise judgment.
2) Storiform fibrosis is defined as spindle-shaped cells, inflammatory cells and fine collagen fibers forming a flowing arrangement. Obliterative phlebitis is defined as fibrous venous obliteration with inflammatory cells. Both are helpful for a diagnosis of IgG4-RD. ① and ③ without ② can only be applied in a case with poor IgG4 and/or IgG staining.
Explanatory note 4: steroid reactivity.
Steroid trial is not recommended. However, if patients do not respond to initial steroid therapy, the diagnosis should be reconsidered.

2020 classification criteria

Table 2. The 2020 Revised comprehensive diagnostic (RCD) criteria for IgG4-RD.

[Item 1] clinical and radiological features

One or more organs show diffuse or localized swelling or a mass or nodule characteristic of IgG4-RD. In single organ involvement, lymph node swelling is omitted.

[Item 2] serological diagnosis

Serum IgG4 levels greater than 135 mg/dl.

[Item 3] pathological diagnosis

Positivity for two of the following three criteria:

① Dense lymphocyte and plasma cell infiltration with fibrosis.

② Ratio of IgG4-positive plasma cells /IgG-positive cells greater than 40% and the number of IgG4-positive plasma cells greater than 10 per high powered field

③Typical tissue fibrosis, particularly storiform fibrosis, or obliterative phlebitis

Diagnosis:

Definite: 1) +2) +3)

Probable: 1) +3):

Possible: 1) +2)

Explanatory note 1: Combination of organ-specific diagnostic criteria*.

Patients with a possible or probable diagnosis by comprehensive diagnostic criteria who fulfill the organ-specific criteria for IgG4-RD are regarded as being definite for IgG4-RD.

*Diagnostic criteria according to the IgG4-related organ:.

① International consensus diagnostic criteria for autoimmune pancreatitis[7], ② IgG4-related lacrimal gland, saliva adenitis diagnostic criteria[8], ③ Diagnostic criteria for IgG4-related kidney disease[9], ④ Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012[10], ⑥Diagnostic criteria for IgG4-related ophthalmic disease[11], ⑥Diagnostic criteria for IgG4-related respiratory disease[12], ⑦ Diagnostic criteria for IgG4-related large periarteritis/periarteritis and retroperitoneal fibrosis[13].

Explanatory note 2: exclusion diagnosis.

1) It is important to acquire tissue samples from each involved organ to distinguish malignant tumors (e.g. cancer, malignant lymphoma) and similar benign conditions (e.g. Sjögren syndrome, primary sclerosing cholangitis, multicentric Castleman's disease, secondary retroperitoneal fibrosis, granulomatosis with polyangiitis, sarcoidosis, eosinophilic granulomatosis with polyangiitis).

2) It is important to exclude an infectious- or inflammation-related disease in patients with high fever, highly elevated CRP and neutrophilia.

Explanatory note 3: pathologic diagnosis.

1) The numbers of IgG4-positive cells are usually more abundant in resected organs and partially enucleated tissue than in tissue samples obtained by needle biopsy or endoscopic biopsy. Thus, it is important to not be too particular about cell number and to provide a precise judgment.

2) Storiform fibrosis is defined as spindle-shaped cells, inflammatory cells and fine collagen fibers forming a flowing arrangement. Obliterative phlebitis is defined as fibrous venous obliteration with inflammatory cells. Both are helpful for a diagnosis of IgG4-RD. ① and ③ without ② can only be applied in a case with poor IgG4 and/or IgG staining.

Explanatory note 4: steroid reactivity.

Steroid trial is not recommended. However, if patients do not respond to initial steroid therapy, the diagnosis should be reconsidered.

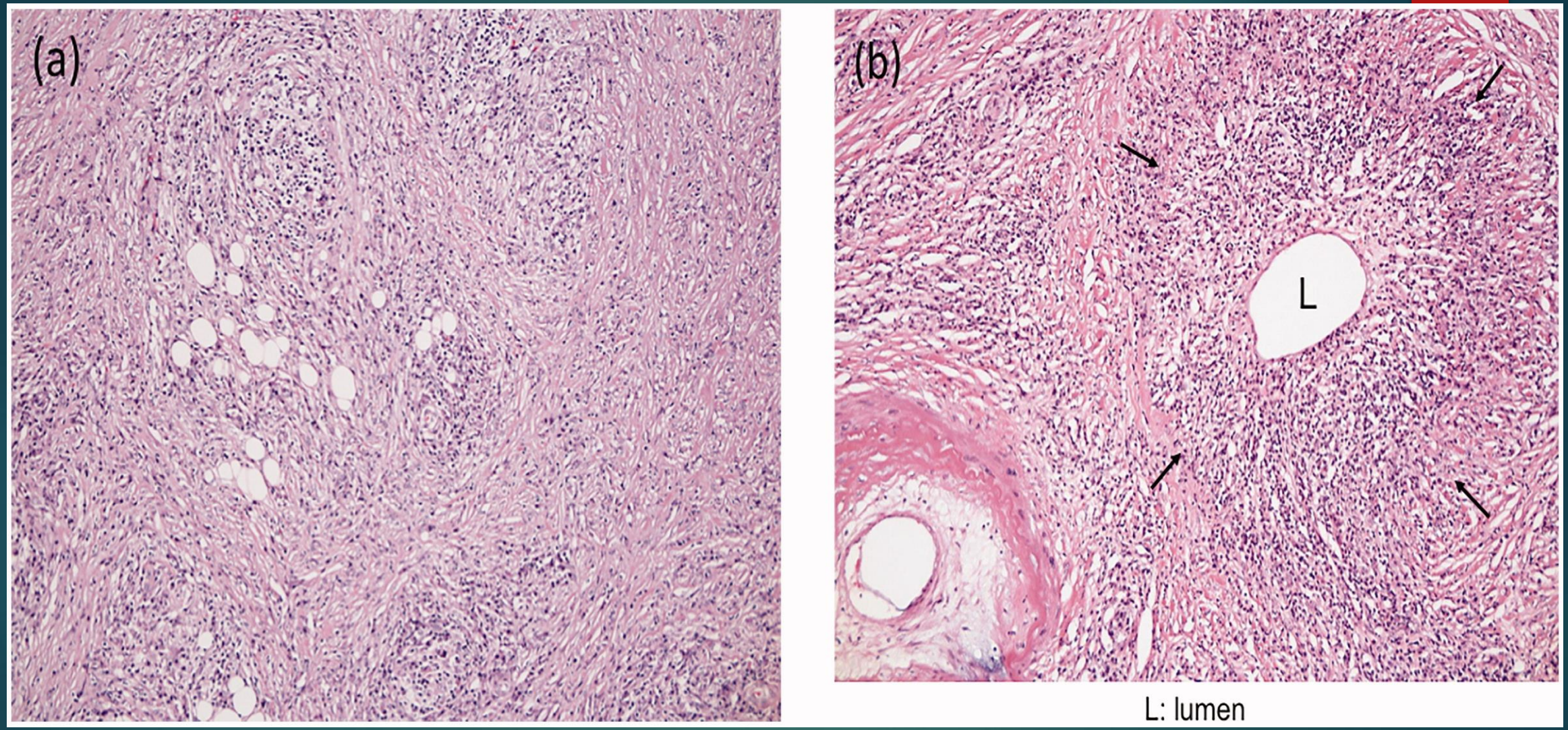
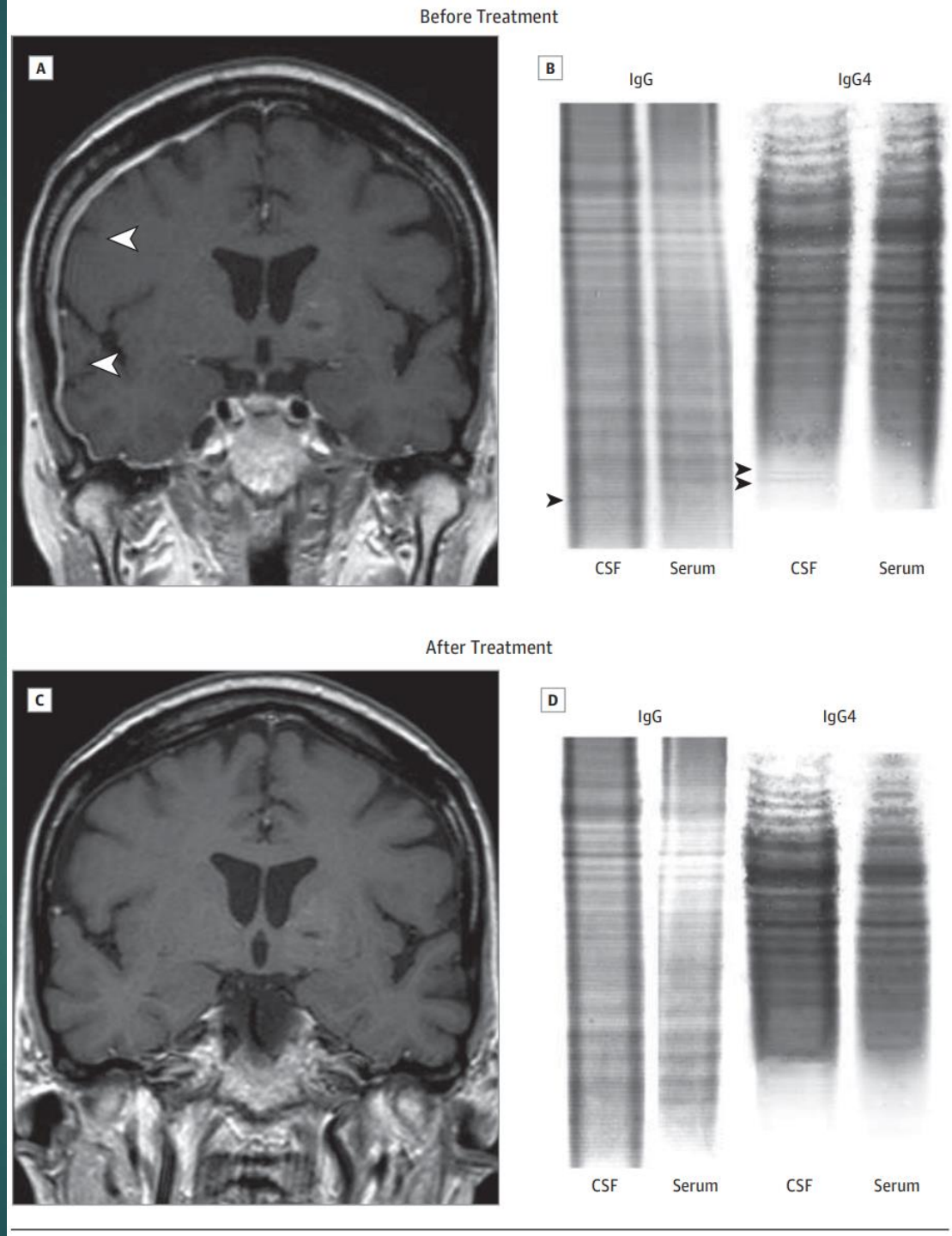


Figure 1. Storiform fibrosis and obliterative phlebitis. (a) Storiform fibrosis: spindle-shaped cells, inflammatory cells and fine collagen fibers are forming a flowing arrangement. The infiltration of plasma cells is easy to recognize. Eosinophils are also intermingled (hematoxylin and eosin stain). (b) Obliterative phlebitis: fibrous venous obliteration with inflammatory cells (arrows). L:lumen.

IgG4-related Hypertrophic pachymeningitis

- Tissue hypertrophy resulting in dural thickness



Symptoms

Table 1. Common Presenting Neurological Features of 33 Patients With IgG4-Related Hypertrophic Pachymeningitis

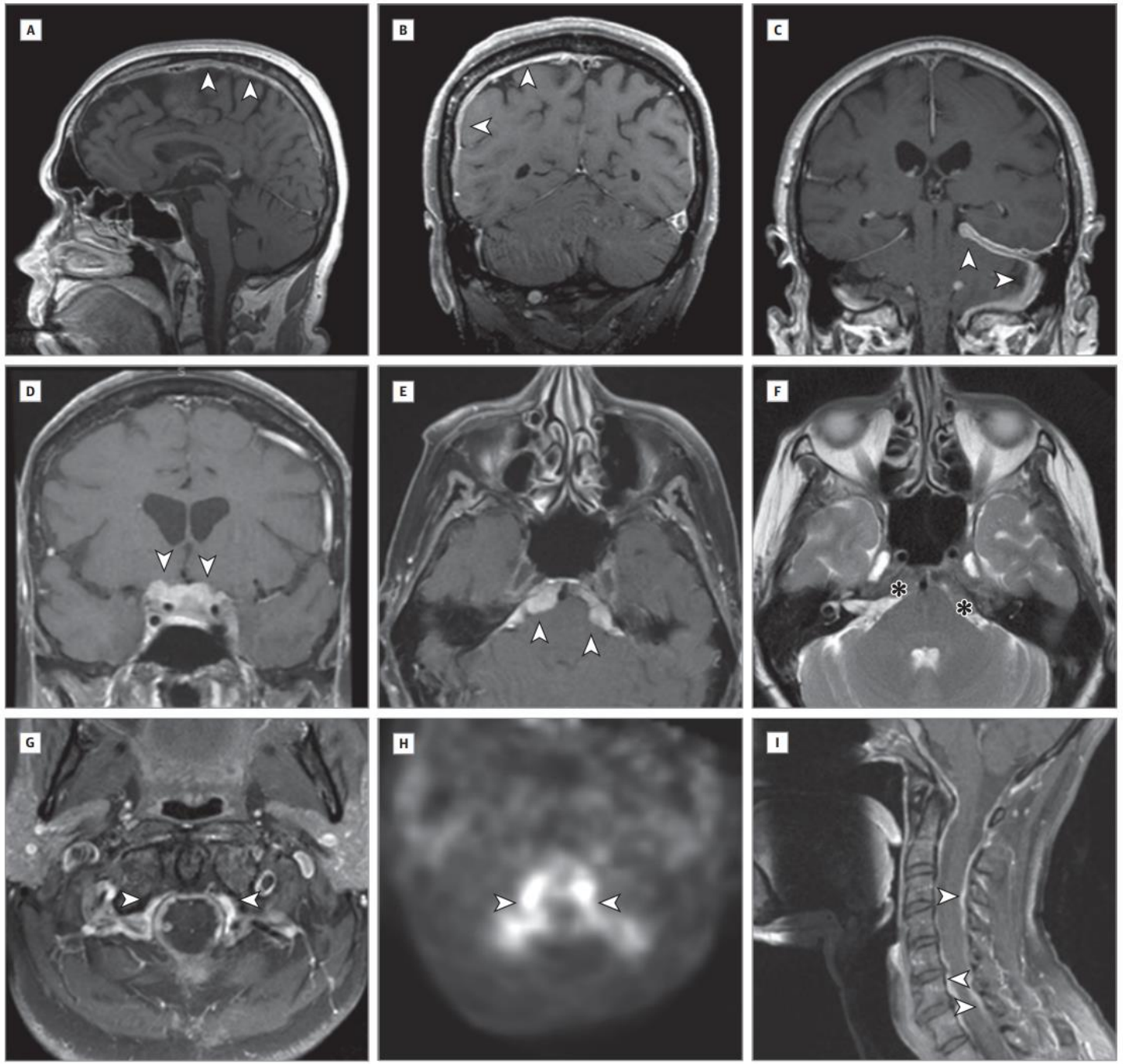
Symptoms and Signs	No. (%)
Headache	22 (67)
Cranial nerve palsies	11 (33)
Vision problems	7 (21)
Motor weakness	5 (15)
Limb numbness	4 (12)
Hearing loss	3 (9)
Seizures	2 (6)
Cognitive decline	1 (3)

Table 2. Associated Common Systemic Features in 33 Patients With IgG4-Related Hypertrophic Pachymeningitis

Organ-System Involvement	No. (%)
None	10 (30)
Unknown	9 (27)
Bone	4 (12)
Salivary glands	3 (9)
Lung	3 (9)
Kidney	2 (6)
Orbital pseudotumor	2 (6)
Retroperitoneal fibrosis	2 (6)

Radiologic features

Figure 3. Radiological Features of IgG4-Related Hypertrophic Pachymeningitis



Serologic features

- Serologic findings in IgG4-RHP may depend on the extent of disease in both the meninges and extra-meningeal organs.
- ESR/CRP – are usually elevated to a moderate degree.
- Increased levels of serum IgE (not always)
- No specific antinuclear antibody
- Elevated serum IgG4 in multiorgan involvement
- IgG4/total IgG ratio (lack of sufficient sensitivity and specificity)

CSF analysis

CSF tapping

Exclusion of CNS infections and malignancies

Normal glucose

Normal to mildly increased protein levels

Variable degree of lymphocytic pleocytosis

Intrathecal oligoclonal band

Higher CSF IgG4 concentration

Higher CSF IgG4 indices.

Higher CSF IgG4 Loc values

Table 3. Features of Lumbar Puncture in IgG4-Related Hypertrophic Pachymeningitis

Parameter[a]	Source[b]									
	Moss et al, 2012	Tajima et al, 2012	Yamashita et al, 2012	Shapiro et al, 2012	Wallace et al, 2013	Lipton et al, 2013	Hyun et al, 2013	Della-Torre et al, 2012 and 2013		
Appearance						Colorless, clear	Colorless, clear	Colorless, clear	Colorless, clear	Colorless, clear
Protein, mg/dL	42, 45	260		83	135, 22	71		44	76	82
Glucose, mg/dL	30, 40					51		59	42	73
White blood cell count, µL (lymphocytes %)	4 (44), 12 (95)	14	25 (86)	23	112 (94), 4 (88)	24 (93)		2 (100)	32 (100)	1 (100)
Cytology[c]	Neg	Neg	Neg			Neg	Neg	Neg	Neg	Neg
Microbiology[d]						Neg	Neg	Neg	Neg	Neg
Oligoclonal bands								Present	Present	Present
CSF IgG, mg/dL							38	8.7	17.4	18.8
IgG index								1.8	0.8	1.8
IgGLoc								5.5	1	12.4
CSF IgG4, mg/dL								4.94	5.36	5.17
IgG4 index								3.16	3.21	3.07
IgG4Loc								4.09	3.91	4.02

Abbreviations: CSF, cerebrospinal fluid; Loc, local immunoglobulin synthesis (according to the Reiber/Felgenhauer formula); Neg, negative.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; IgG to grams per liter, multiply by 0.01; lymphocytes to $\times 10^9$ per liter, multiply by 0.001.

[a] Reference ranges are as follows: normal values for protein = 12-60 mg/dL, glucose = 40-80 mg/dL, white blood cell count = 0-1/µL, ogliclonal bands = absent, CSF IgG = 0.8-3.8, IgG index = <0.7, IgGLoc = 0, CSF Ig4 = 0.01-0.33 mg/dL, IgG4 index = 0.25-2.11, and IgG4Loc = 0.

[b] See eReferences in Supplement.

[c] Morphological and flow cytometry analysis for malignant cells.

[d] Bacterial, fungal, and mycobacterial cultures as well as Venereal Disease Research Laboratory test, polymerase chain reaction for herpes simplex virus, and cryptococcal antigen.

$$\text{IgG Index} = \frac{\text{CSF IgG / Serum IgG}}{\text{CSF albumin/Serum albumin}} = \text{normal} < 0.7$$

Measures intrathecal synthesis of IgG

$$\text{IgG (loc)} = \text{normal} < 0$$

$$[a/b] - 0.8\sqrt{(b/d)^2 + 15 \times 10^{-6}} + [1.8 \times 10^{-3}]\, c$$

a- CSF IgG; b- CSF Albumin; c- Ser IgG; d- Ser Albumin

Measure is the same as IgG synthetic rate, but should be used when the (BBB) Q albumin is abnormally high

IgG4 index and IgG4 Loc

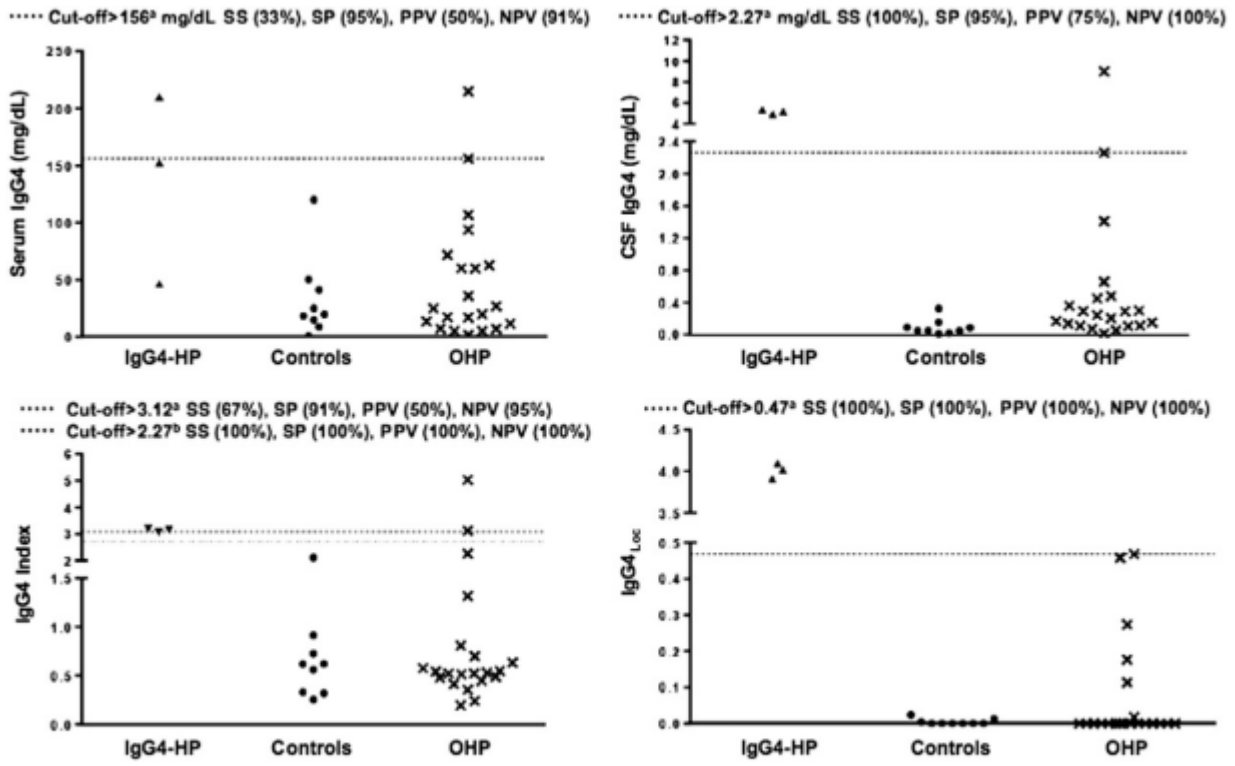


Fig. 1. Scatterplot for serum and CSF IgG4, IgG4 Index and $IgG4_{LOC}$ in the three different groups (n). IgG4-HP(3), Control subjects(9) and patients with Other form of Hypertrophic Pacymeningitis (OHP)(21). Cut-off values were calculated as **(a)** the 95th percentile of subjects with OHP ($n = 21$) and **(b)** the 95th percentile of subjects with OHP without including infectious form of HP ($n = 17$).

IgG4Loc values higher than 0.47 achieved 100% of both sensitivity and specificity in differentiating IgG4-HP from OHP.

$$\text{IgG Index} = \frac{\text{CSF IgG / Serum IgG}}{\text{CSF albumin/Serum albumin}} = \text{normal} < 0.7$$

Measures intrathecal synthesis of IgG

$$\text{IgG (loc)} = \text{normal} < 0$$

$$[a/b] - 0.8\sqrt{(b/d)^2 + 15 \times 10^{-6}} + [1.8 \times 10^{-3}]\, c$$

a- CSF IgG; b- CSF Albumin; c- Ser IgG; d- Ser Albumin

Measure is the same as IgG synthetic rate, but should be used when the (BBB) Q albumin is abnormally high

Treatment

- Currently no consensus about treatment
- Steroid therapy
  - In AIP, Pd (0.6mg/kg/d for 4wks), 3-6months tapering to maintenance dose of 2.5-5.0mg/d for up to 3 years
  - In case of severe neurologic compromise, pulse dose of methylPd (1g/day for 3 consecutive days)
- Steroid-sparing agents
  - MTX, Azathioprine, Mycophenolate mofetil, Cyclophosphamide
- Rituximab

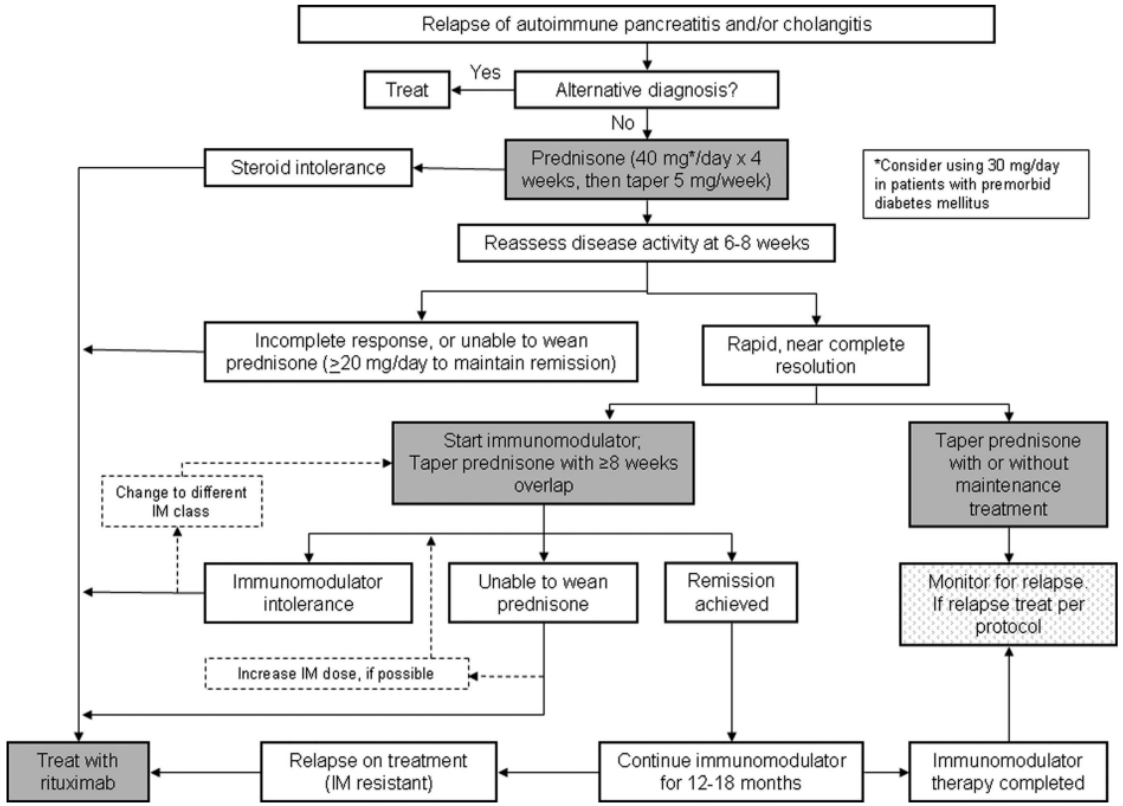


Figure 3 Mayo Clinic treatment algorithm for management of disease relapses for patients with firmly established (ie, cancer has been excluded) autoimmune pancreatitis and/or IgG4-related sclerosing cholangitis.

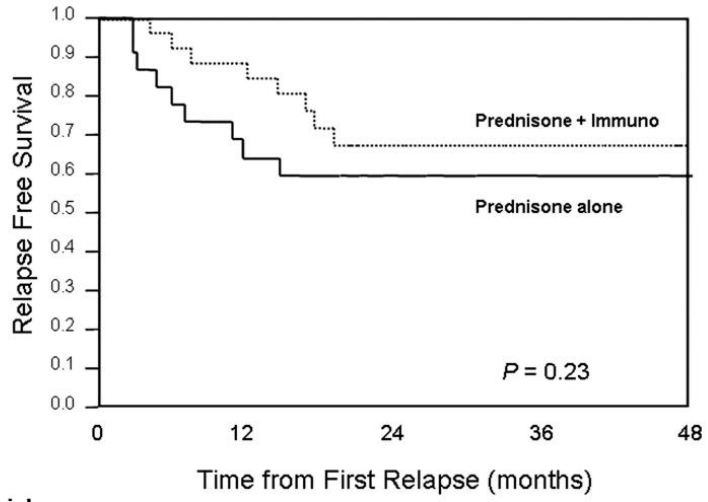


Table 1 Treatment protocols used for steroid, immunomodulator and rituximab (RTX) therapy

	Induction regimen	Taper	Maintenance
Steroids	Prednisone 40 mg daily×4 weeks	5 mg/wk until discontinued	None
Immunomodulator	Azathioprine 2.0–2.5 mg/kg/day (alternate: 6-MP 1 mg/kg/day) (alternate: MMF 750–1000 mg twice daily)	N/A	Continue×12–18 months
RTX	375 mg/m^2 intravenous BSA weekly×4 weeks Coadminister: oral diphenhydramine 50 mg and oral paracetamol 1000 mg once	N/A	Repeat infusions every 2–3 months×24 months (total of 8 additional doses)

6-MP, 6-mercaptopurine; BSA, body surface area; MMF, mycophenolate mofetil.

감사합니다!