

폐외결핵의 진단과 치료

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27세 여자

- 2개월동안 항결핵제 치료 도중 목에 림파선 오히려 더 커지는 증상으로 내원
- 외부병원 검사
 - Bx: chronic granuloma with necrosis
 - AFB (-) MTB PCR (-) MTB culture not done
- 2개월간 HREZ를 꾸준히 복용

질문

- 진단은 결핵성 림파선염이 맞는가?
 - 병리조직에서 결핵인데도 AFB (-) MTB PCR (-) 일 수 있는가?
 - 결핵배양 검사는 꼭 필요한가?
 - 추가로 시행했어야 할 검사는?
- 향후 계획은?
 - 항결핵제 유지 또는 교체?

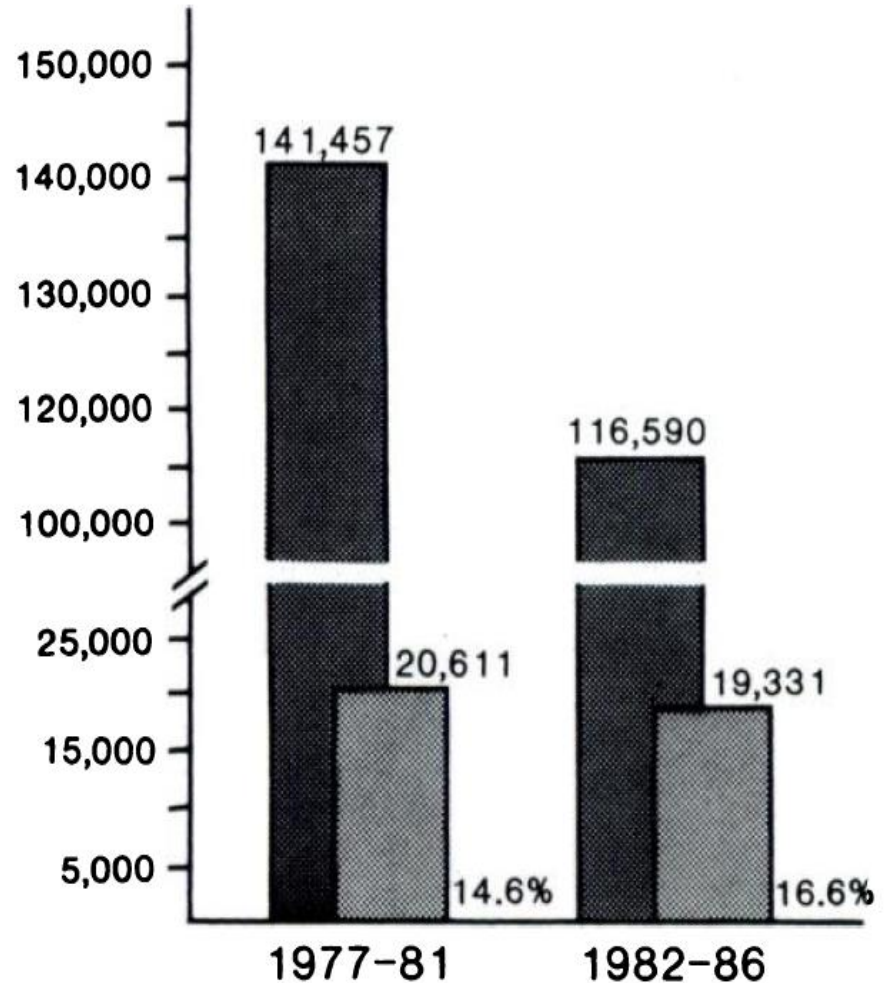
폐외결핵의 역학적 특성

- 폐외결핵 환자의 숫자는 일정하게 유지

60년대	80년대	90년대
7%	→ 18%	→ 20%

Schlossberg D. TB & NTM Infects textbook

- 폐외결핵 위험인자
 - AIDS
 - 면역억제제 사용
 - Asians



폐외결핵

- 우리나라에서 전체 결핵 중 약 20%
- TB pleurisy
- TB lymphadenopathy
- TB peritonitis, intestinal TB
- Musculoskeletal TB
- TB meningitis
- Genitourinary TB
- TB pericarditis

폐외결핵

- 미생물학적 검사를 위하여 침습적 검사가 필요하다.
- 침습적 검사로 얻어진 조직에 mycobacterial burden이 적다.
- AFB stain 양성률이 낮으며, 배양검사는 경험적 치료 시작에 도움을 주지 못 한다.
- 조직학적 소견과 방사선학적 소견이 도움이 되지만 다른 질환에서 비슷한 소견이 나타날 수 있다.

TB lymphadenopathy

- 폐외결핵의 가장 흔함(미국 자료에서 전체 폐외결핵의 40%이상)
- 여자가 많음
- 40%이상에서 폐결핵 또는 다른 폐외결핵 동반
- 진단은 FNABx or surgical bx
 - AFB smear, culture
 - *M. TB* PCR
 - Chronic granuloma with/without caseating necrosis

Diagnostic yield of conventional tests

Characteristic	Final Diagnosis	
	Extrapulmonary Tuberculosis ^b (n = 32)	Not Tuberculosis (n = 35)
Results of diagnostic tests for tuberculosis		
Granulomatous inflammation seen in biopsy specimen	22 (69) ^f	3 (9) ^g
Positive acid-fast bacilli stain in biopsy specimen	5 (16)	0
Positive <i>Mycobacterium tuberculosis</i> polymerase chain reaction in biopsy specimen	15 (47)	0
Positive <i>M tuberculosis</i> culture in biopsy specimen	18 (56)	0

^gBiopsy specimens were available in 25 patients. Of 3 patients with chronic granulomatous inflammation, 2 were diagnosed as having fungal infections and 1 as having brucellosis.

Paradoxical response

- 림파선 결핵에서 흔하지만, 다른 폐외결핵에서도 나타남
- 치료 도중 20-30% 발생
- 치료 후 2주에서 8개월에 호발(대부분 12주 이내)
- 감별진단
 - Noncompliance
 - 진단 잘못
 - 내성 결핵
- IRIS (immune reconstructive inflammatory syn)
 - Paradoxical TB-associated IRIS
 - unmasking TB-associated IRIS

41 year-old woman

9개월 전 Lt. cervical LN enlargement 발생하여 시행한 Biopsy 결과
Chronic granulomatous inflammation with caseous necrosis 소견 보였다.
AFB stain/culture 상 균 확인되지 않았으나 항결핵제 복용 시작하였다.

5개월 전 (치료 4개월 경과) Lt. cervical LN 크기가 더 증가하였고
2개월 전 Paradoxical response로 판단하여 PD 60mg 시작하였다.
당시 Biopsy 결과 Necrosis with spindle cell proliferation 확인되었다.

1개월 전 PD 30mg로 감량하여 유지 중에도 Lt. cervical LN swelling 악화,
Rt. Cervical LN enlargement 새로 발생하여 본원 의뢰되었다.

Physical Examination



치료 4개월째

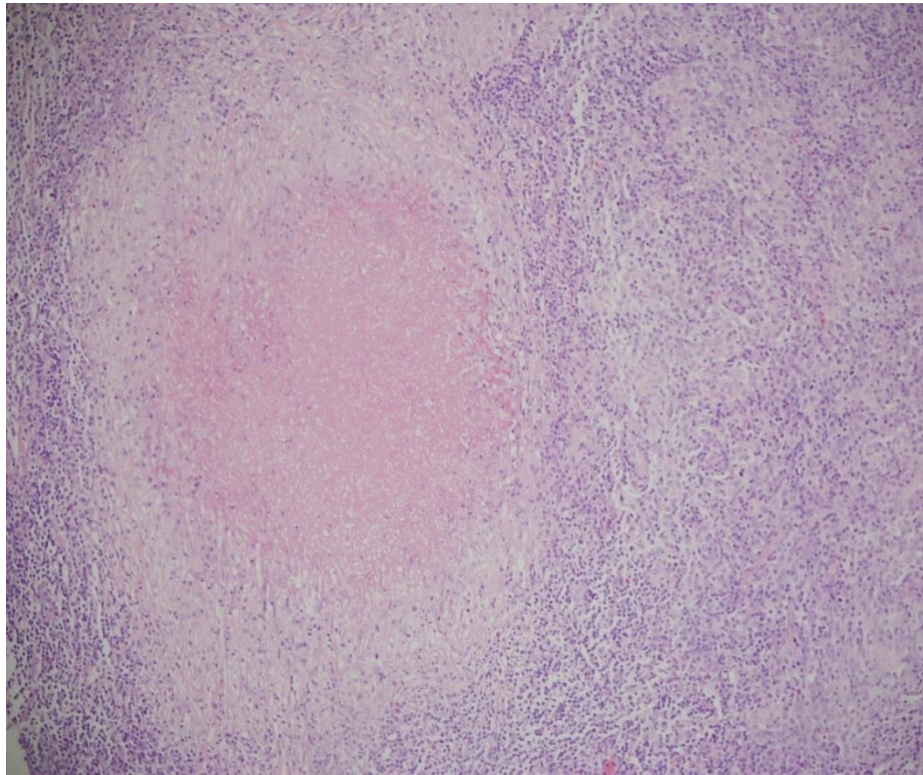


치료 9개월째

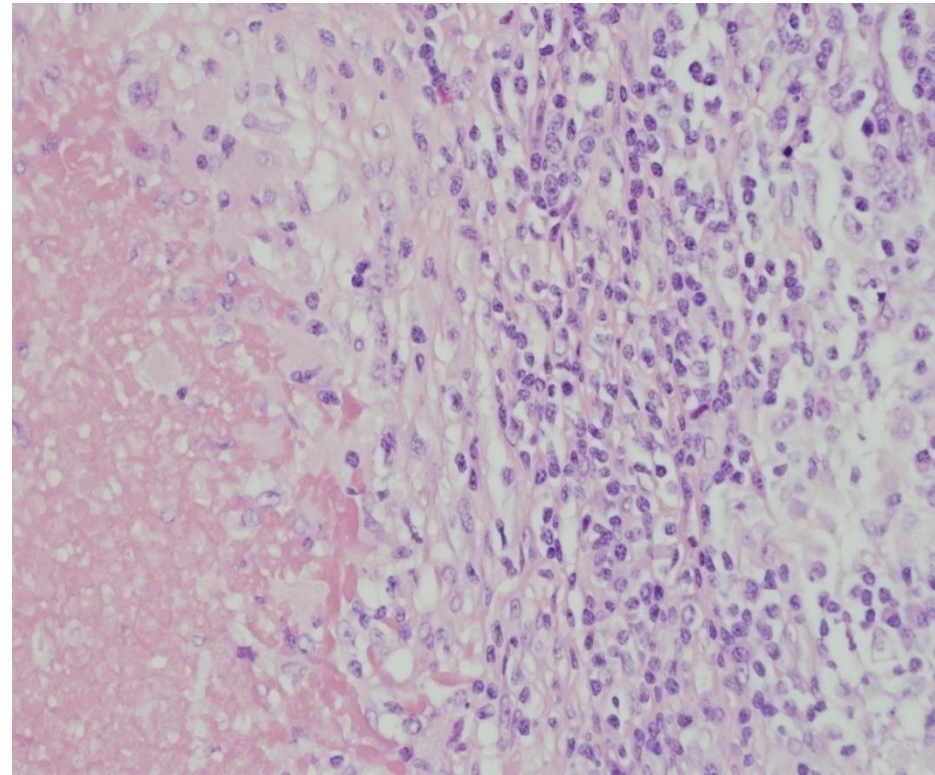


Outside slide review (Lt. cervical LN, 9MA)

: Chronic granulomatous inflammation with caseous necrosis

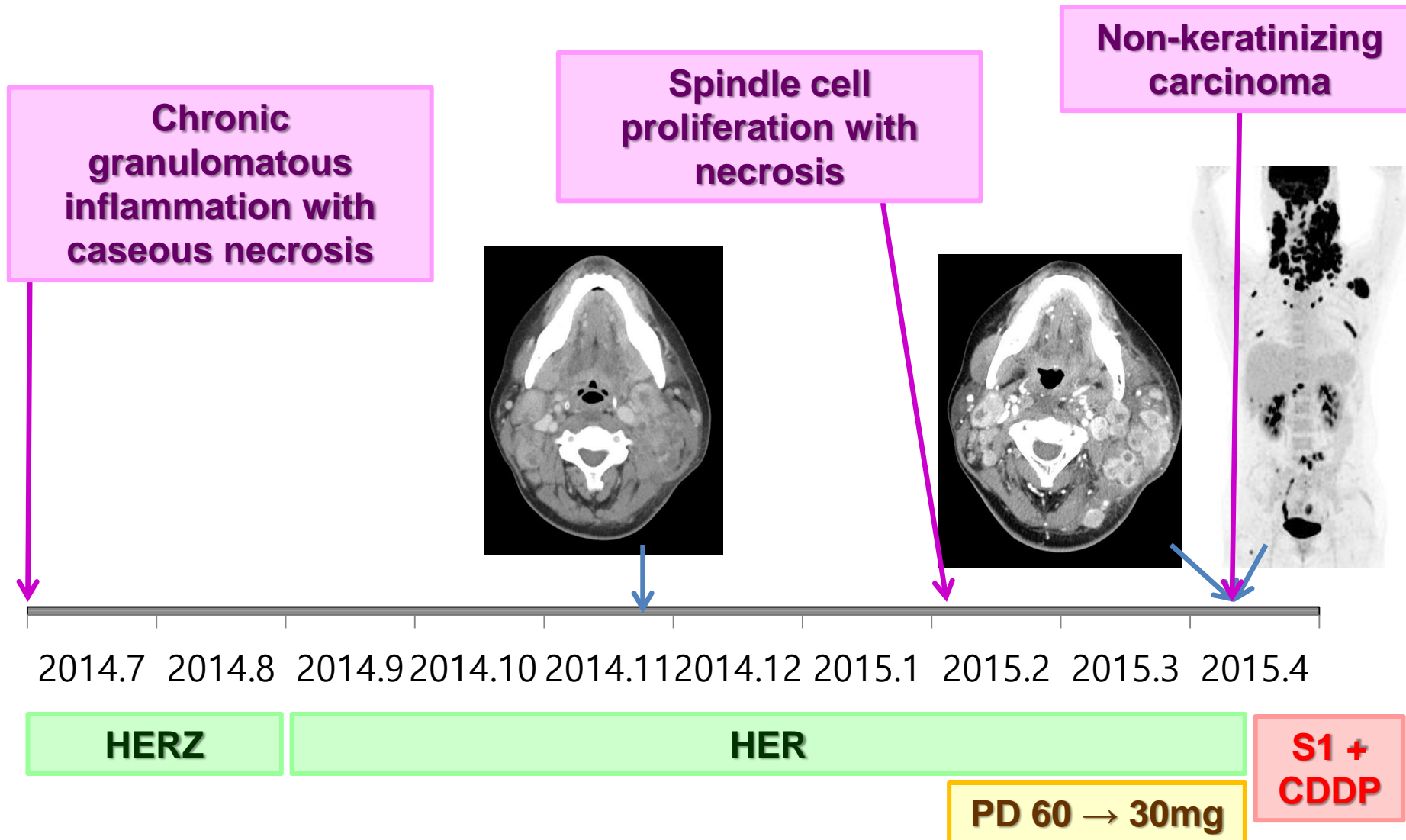


H&E (x100)



H&E (x400)

Summary



Drug resistance in E-TB

- 내성률이 폐결핵과 유사?
 - 내성균은 병독성이 떨어져서 폐외로 잘못간다?
 - 폐외결핵은 대부분 과거 감염이 잠복상태에서 재활성화 → 과거 내성패턴?
- 캐나다: single resistance 15.1% (폐결핵 16.7%)
- 미국: 다제내성률 0.9% (폐결핵 1.6%)
- 우리나라: 다제내성률 15% (폐결핵 23%)

Yang H, et al. *Int J Tuberc Lung Dis* 2005;9:288-93
Peto HM, et al. *Clin Infect Dis* 2009;49:1350-7
Kim MJ, et al. *J Korean Med Sci* 2009;24:237-41

MDR 1.8%

Drugs resistance pattern	Cases (%) N=168	Infection sites
Any resistance	15 (8.9)	
INH	4 (2.4)	Colon (n=2), Skeletal (n=1), Peritoneal (n=1)
SM	2 (1.2)	Lymph node(n=1) , Miliary with CNS (n=1)
OFX	1 (0.6)	Genitourinary
INH+SM	1 (0.6)	Miliary with CNS
EMB+PAS	1 (0.6)	Peritoneal
INH+PZA+PTH	1 (0.6)	Lymph node
INH+EMB+SM	1 (0.6)	Pleural
INH+PTH+SM	1 (0.6)	Lymph node
INH+RMP+EMB	1 (0.6)	Lymph node
INH+RMP+EMB+PZA	1 (0.6)	Genitourinary with pulmonary
INH+RMP+EMB+PZA+PTH+KM	1 (0.6)	Miliary

Relapsed TB LAP

Table 1. Diagnosis and Treatment of Rifampin-resistant Relapsed Tuberculosis Cases

	Case 1	Case 2
Sex/Age	F/38	M/38
Type of TB	cervical TB lymphadenitis	liver, spleen and peritoneal TB
Diagnosis of TB		
AFB stain	(+) from biopsy tissue	(+) from biopsy tissue
TB culture	(-) from biopsy tissue	Not done
TB-PCR	(+) from biopsy tissue	Not done
Anti-TB treatment		
Anti-TB drug susceptibility test	Not done	Not done
Anti-TB drug	INH+RFP+EMB+PZA	INH+RFP+EMB+PZA
Treatment duration	6 months	9 months
Recurrent symptom onset duration after anti-TB Tx.	4 months	4 months
Diagnosis of recurrent TB		
AFB stain	(+) from biopsy tissue	(-) from biopsy tissue
TB culture	(-) from biopsy tissue	(-) from biopsy tissue
TB-PCR	(+) from biopsy tissue	(+) from biopsy tissue
Treatment for recurrent TB		
Anti-TB drug susceptibility test	DNA line probe assay (GenoType® MTBDRplus)	DNA line probe assay (GenoType® MTBDRplus)
Result of drug susceptibility test	INH : susceptible RFP : resistant	INH : susceptible RFP : resistant
Anti-TB drug	INH+EMB+PZA (2 months) INH+EMB (16 months)	INH+EMB+PZA+Moxifloxacin
Treatment duration	18 months	18 months
Outcome/duration of follow up	Recovered/3 months	Transferred state

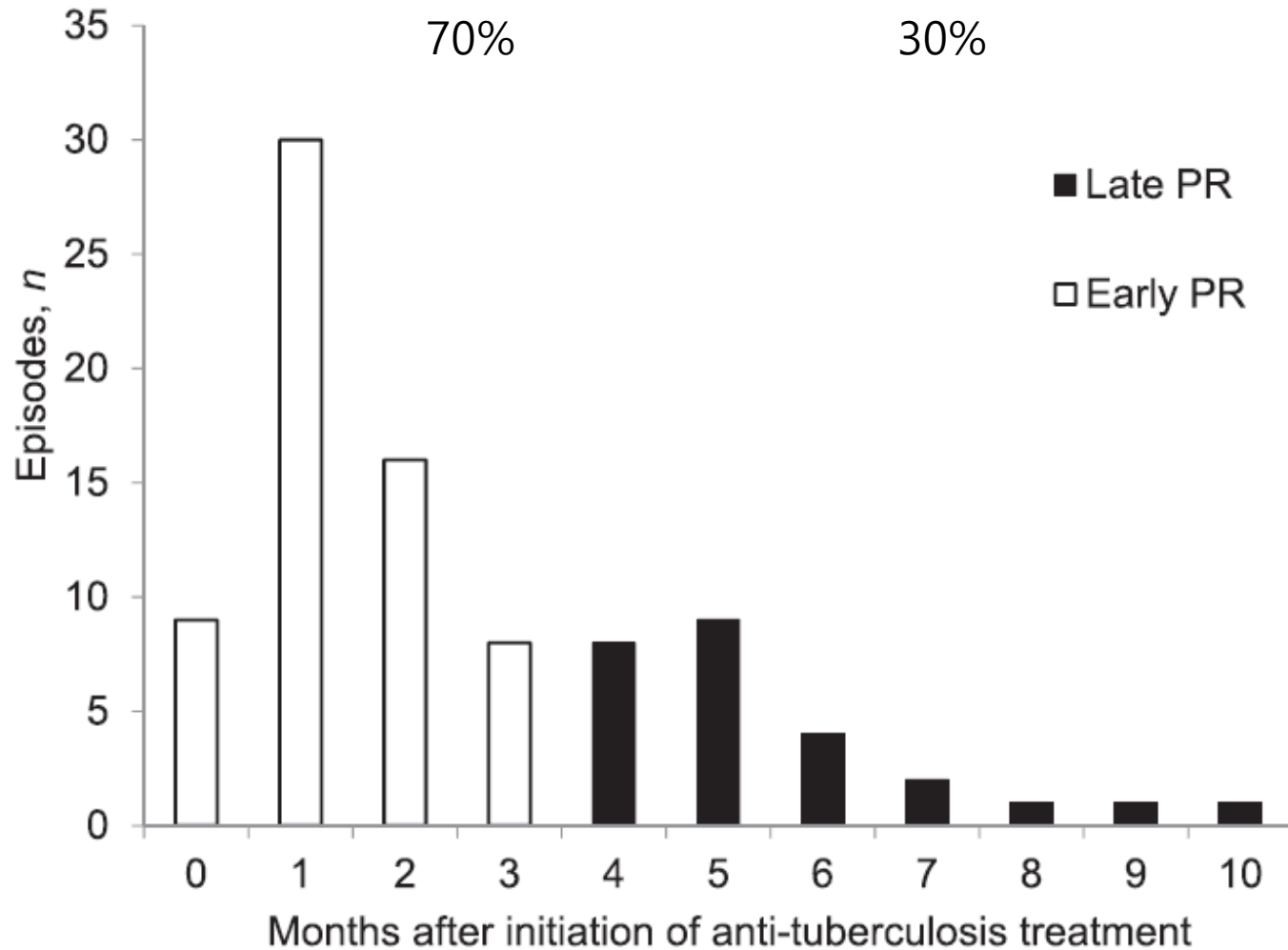
PR 23%

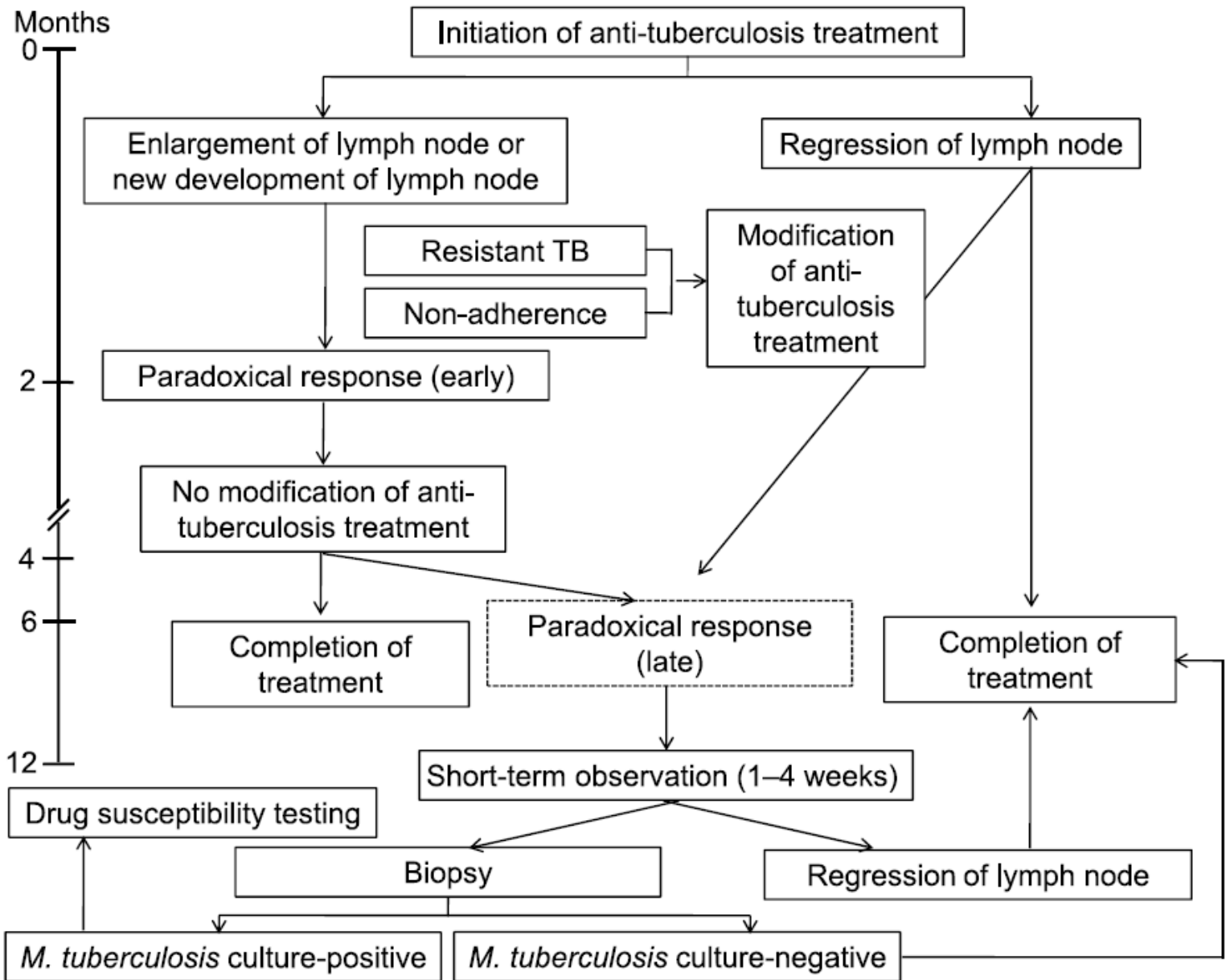
Characteristic	Value
Time to onset of paradoxical response, median weeks (interquartile range)	8 (4–14)
Nature of paradoxical response	
Enlargement only, <i>n</i> (%)	17 (32)
Discharging sinus, <i>n</i> (%)	14 (26)
Enlargement and discharging sinus, <i>n</i> (%)	8 (15)
New nodes at same site with or without discharging sinus, <i>n</i> (%)	5 (9)
New nodes at other sites with discharging sinus, <i>n</i> (%)	7 (13)
New nodes at other sites without discharging sinus, <i>n</i> (%)	3 (6)

PR

Treatment	
Steroid, <i>n</i> (%)	2 (4)
Aspiration, <i>n</i> (%)	10 ^a (19)
Excision, <i>n</i> (%)	12 ^b (27)
Observation, <i>n</i> (%)	30 (56)
Rebiopsy, <i>n</i> (%)	21 (39)
Results of rebiopsy	
AFB-positive, <i>n/N</i> (%)	7/21 (33)
TB PCR-positive, <i>n/N</i> (%)	6/11 (55)
<i>M. tuberculosis</i> culture-positive, <i>n/N</i> (%)	0/6 (0)
Histology	
Granuloma with or without necrosis, <i>n</i> (%)	17/21 (76)
Necrosis or inflammation, <i>n</i> (%)	5/21 (24)

Late PR

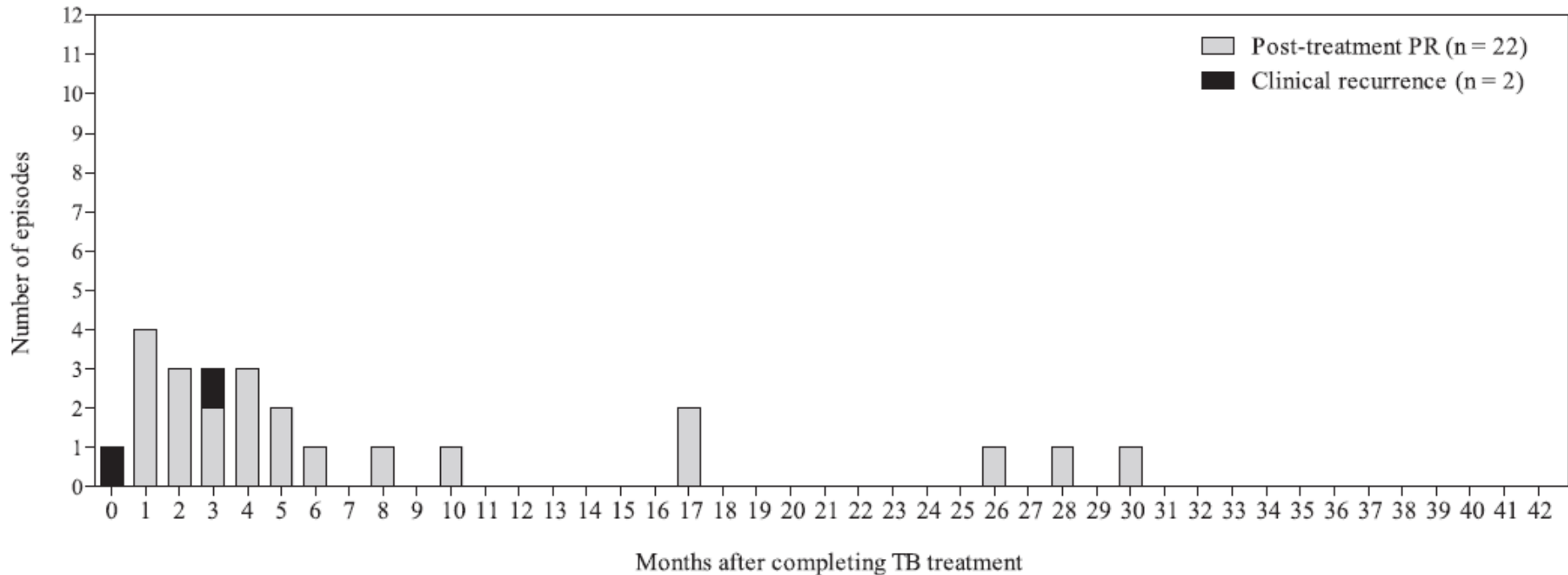




Post-therapy PR (PTPR)

154 TB LAP → post-therapy LAP 24 (16%)

Of 24 patients, 22 (92%) PTPR vs 2 (8%) clinical recurrence

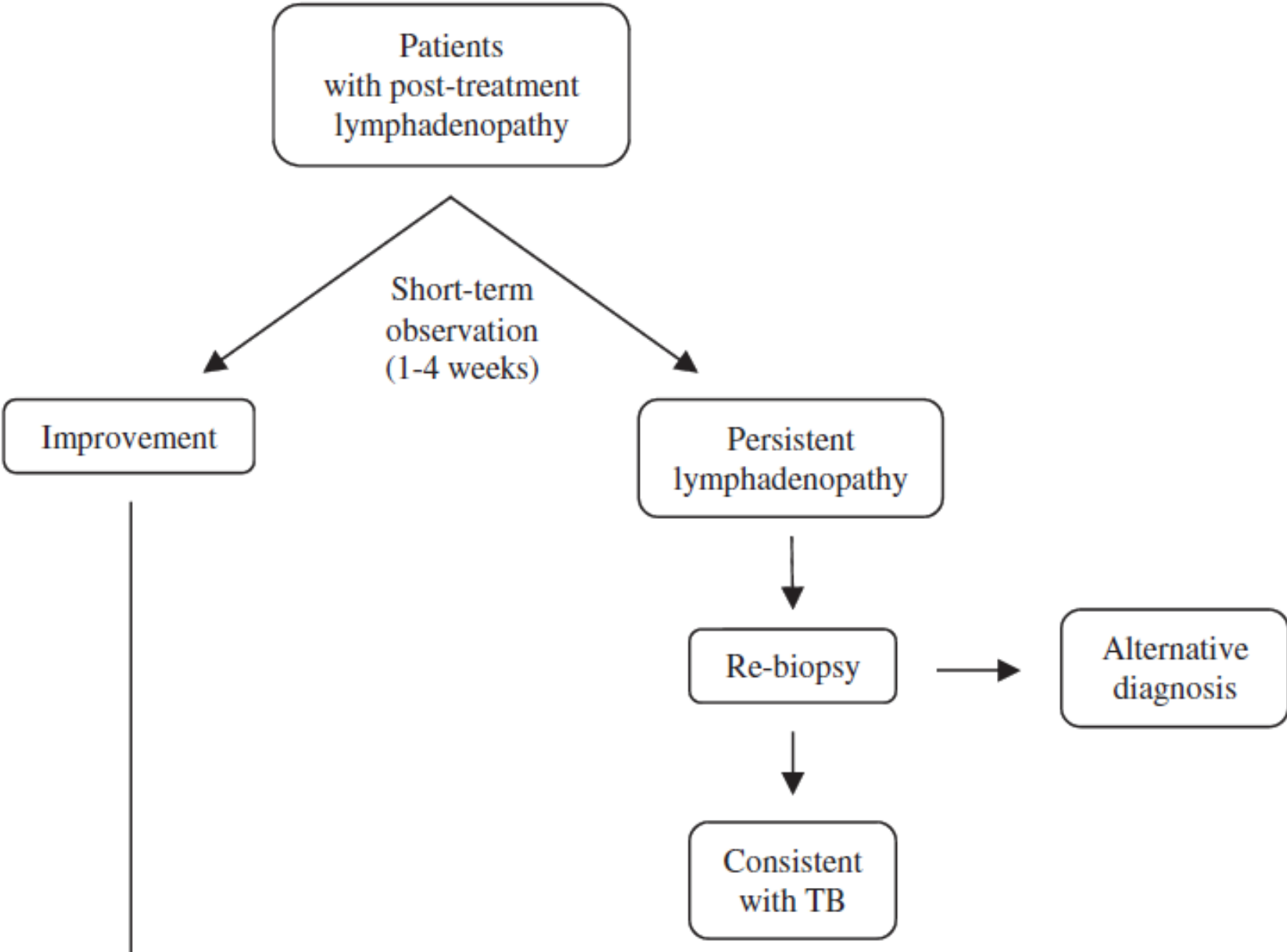


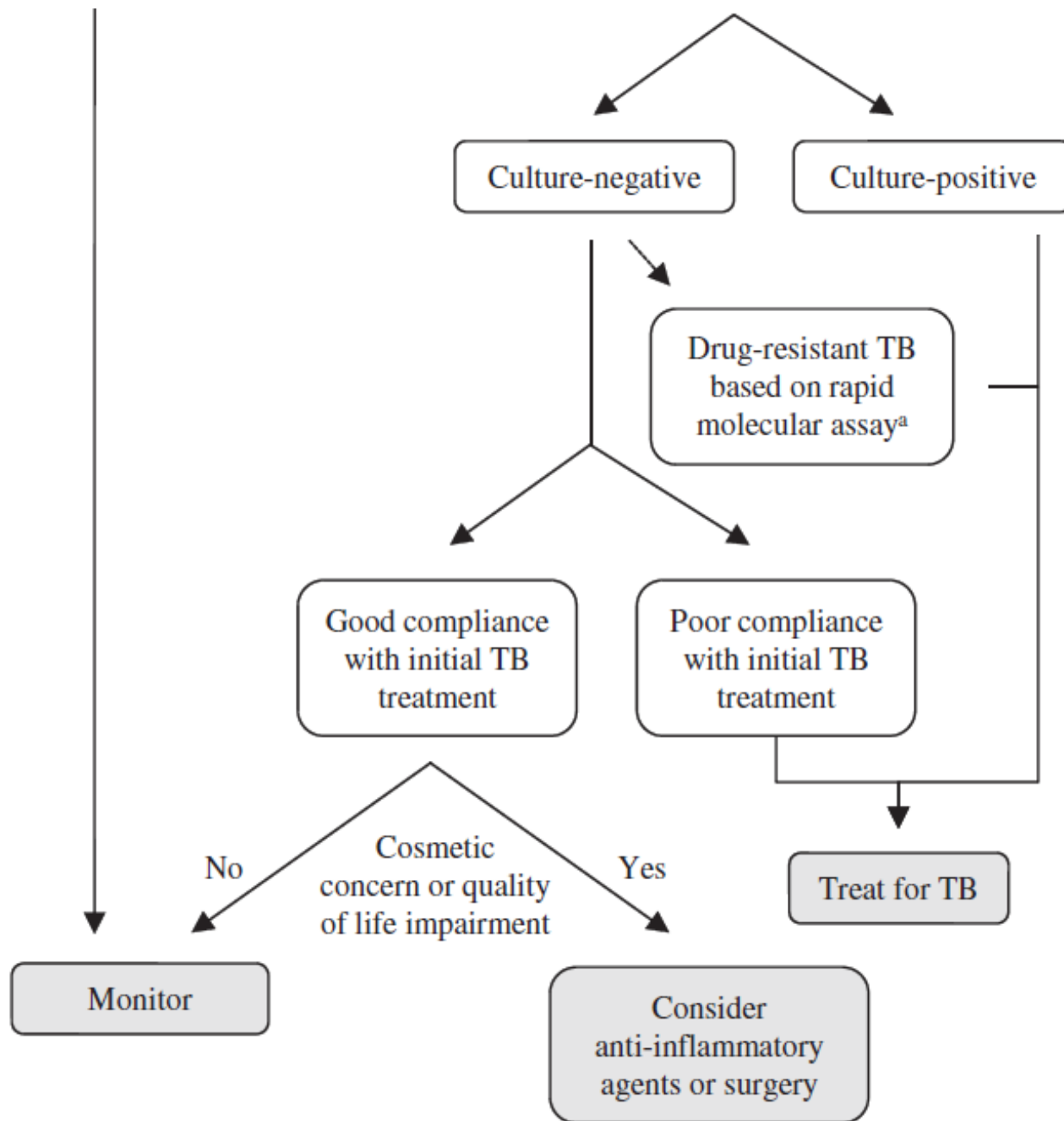
PTPR

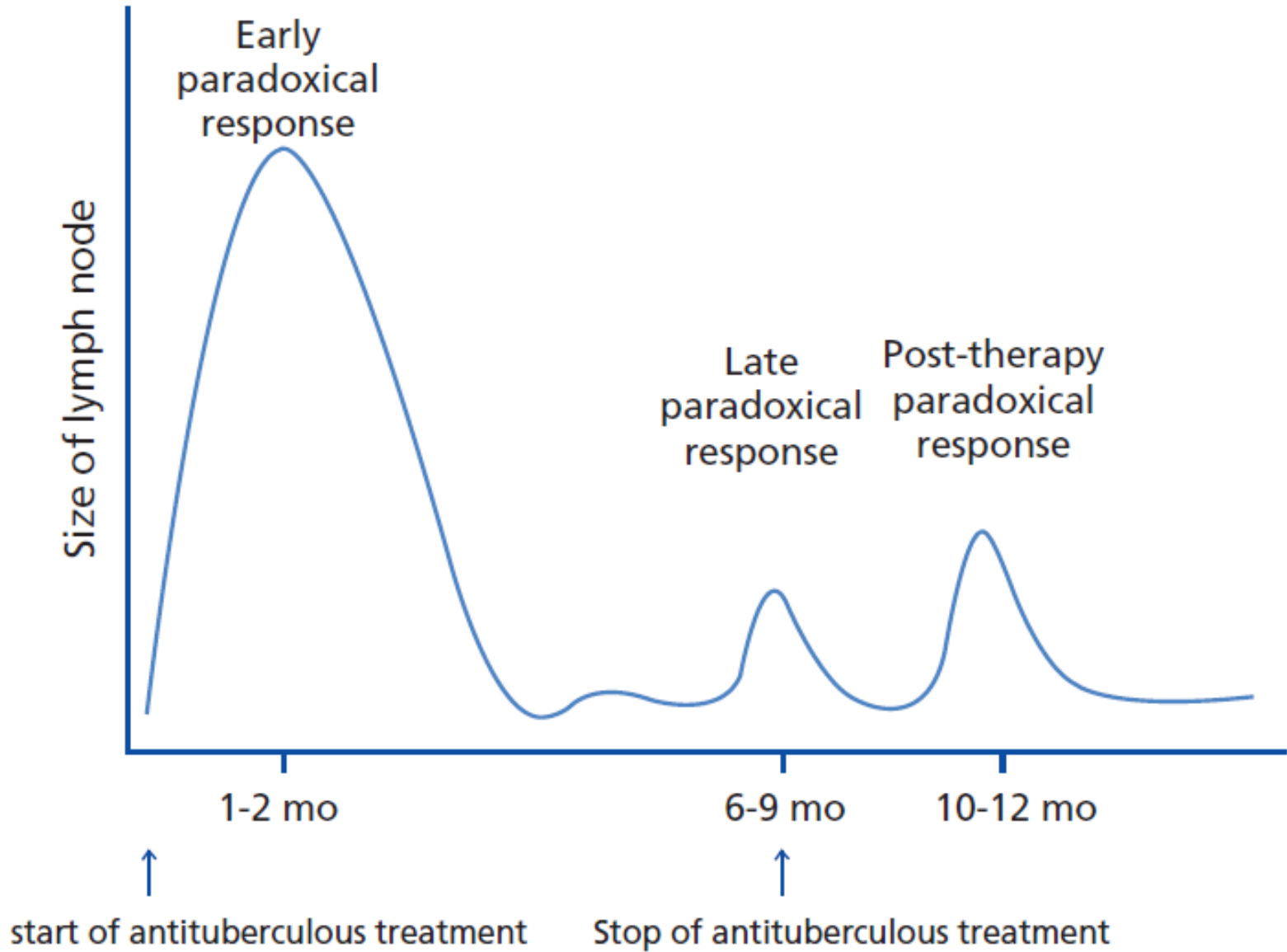
Transfer 환자 포함



Characteristic	All cases (n = 36)
Results of lymph node re-biopsy	
Positive AFB stain	4/23 (17.4)
Positive <i>M. tuberculosis</i> PCR	11/23 (47.8)
Positive culture for <i>M. tuberculosis</i>	0/23 (0)
Histological findings	
Granuloma with necrosis	9/23 (39.1)
Granuloma without necrosis	3/23 (13.1)
Necrosis or inflammation	11/23 (47.8)
Positive IGRA	12/13 (92.3)
Type of treatment	
Steroid	1 (2.8)
Aspiration	2 (5.6)
Excision	1 (2.8)
Retreatment with TB medication	2 (5.6)
Outcomes	
Post-treatment PR	33 (91.7)
Clinical recurrence	3 (8.3)
Microbiological recurrence	0 (0)
Duration of post-treatment lymphadenopathy, median weeks (IQR)	13 (4–27)







Cosmetic outcome



TB meningitis (TBM)

- 폐외결핵의 5-10%
- 50%에서 중추신경이외에서 결핵의 증거가 있음
- 50-70% 환자가 20세 이하에서 생김
- 치료하지 않으면 3개월 내에 모두 사망(평균 4-6주 내에 사망)
- 치료하는 경우 사망률 20-50%, 신경학적 후유증 20-30%

Spectrum of CSF profiles

virus

TB/fungus

bacterial

enterovirus VZV

TB

brucella listeria pneumococcus

HSV?

cryptococcus

WBC

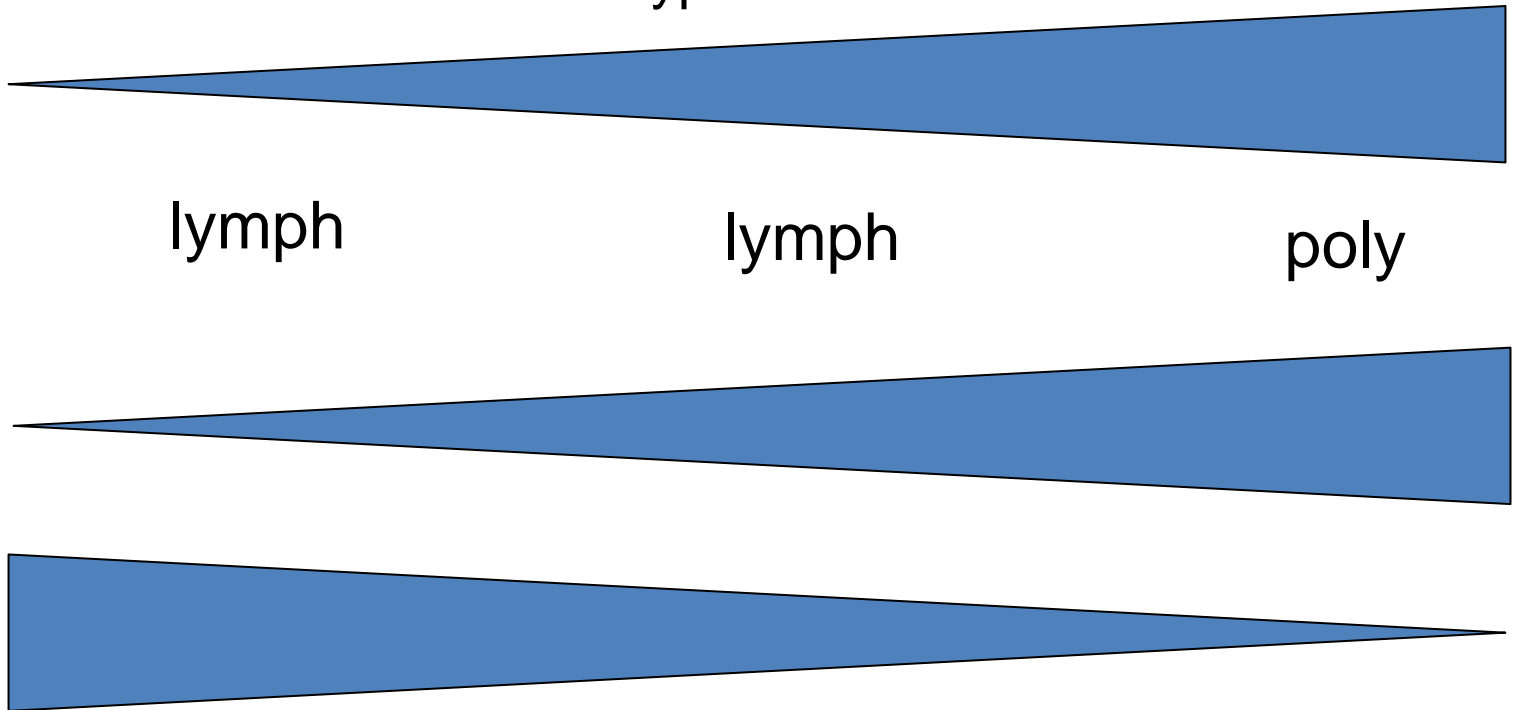
lymph

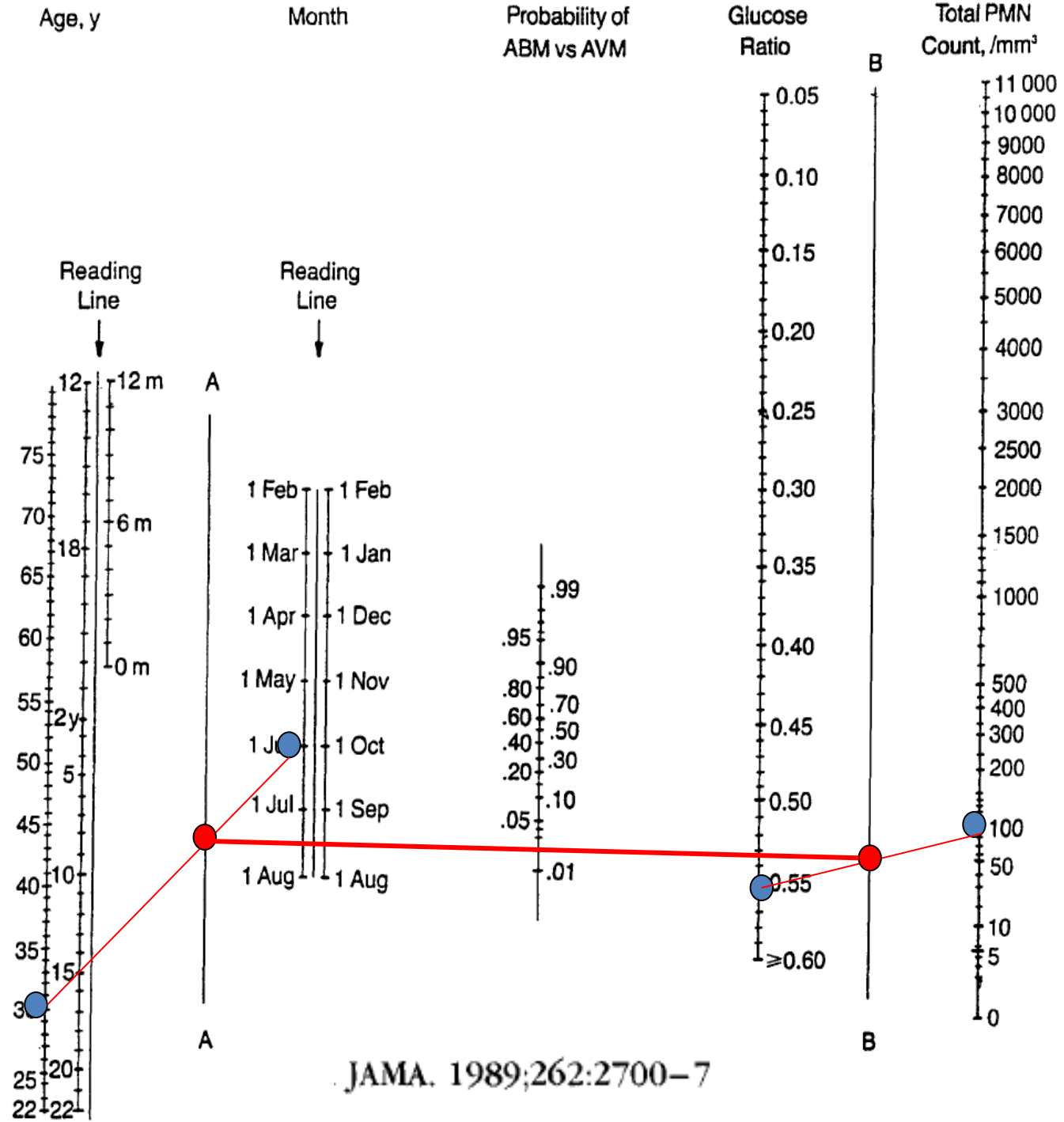
lymph

poly

Protein

Glucose





Bacterial vs TB meningitis

- Incidence: 4~7/100,000 (*BMC ID* 2013;13:108)
 - cf) TBM: TB 100/100,000 → 30% E-TB
30/100,000 → 10% TBM 3/100,000

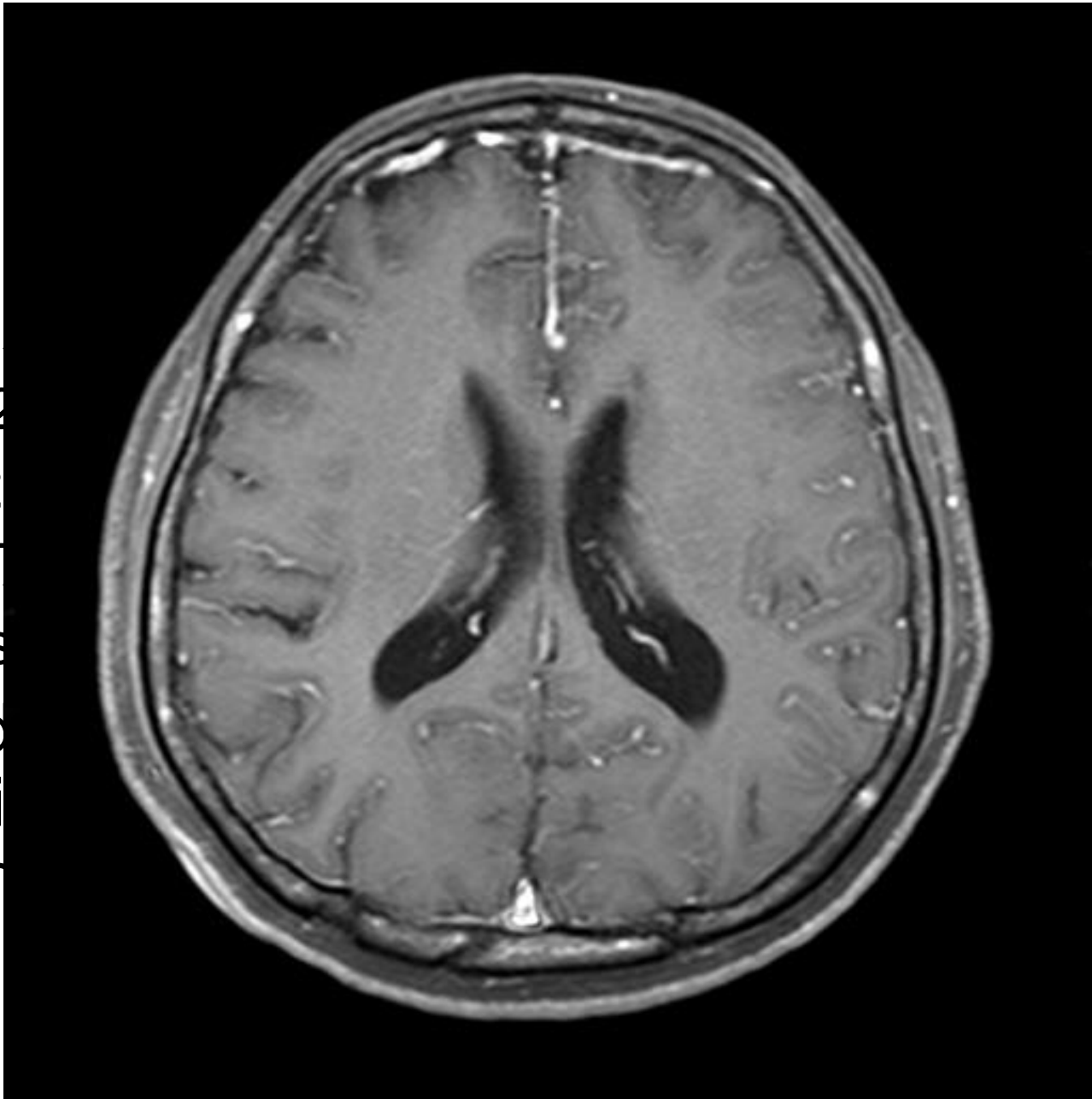
TBM 진단 임상 예측모델

Variable	Score
Age (years)	
>36	2
≤36	0
Blood WCC (10³/ml)	
>15000	4
≤15000	0
History of illness (days)	
≥6	-5
<6	0
CSF total WCC (10³/ml)	
≥750	3
<750	0
CSF % neutrophils	
≥90	4
<90	0

- 4점이하 → TBM, 5점이상 → non-TBM

	VZV without TB medication (Group 1, n=63)	VZV with TB medication (Group 2, n=16)	TB (Group 3, n=24)	P-value		
				Group 1 vs Group 2	Group 2 vs Group 3	P for trend
Clinical manifestations						
Cutaneous zoster	25 (40)	1 (6)	0	0.01	0.40	<0.001
Altered mental status	6 (10)	6 (38)	17 (71)	0.01	0.04	<0.001
Seizure	2 (3)	0	5 (21)	> 0.99	0.07	0.009
Clinical diagnosis, n (%)				0.001	0.29	<0.001
Meningitis	56 (89)	8 (50)	8 (33)			
Encephalitis	7 (11)	8 (50)	16 (67)			
CSF findings						
WBC (cell/mm ³)	230 (65 - 500)	201 (93 - 419)	213 (123 - 383)	0.51	0.69	0.55
Neutrophil, %	1 (0 - 6)	2 (0 - 10)	26 (11 - 61)	0.56	<0.001	<0.001
Lymphocyte, %	79 (58 - 89)	83 (54 - 91)	60 (27 - 74)	0.61	0.17	0.03
Monocyte, %	14 (7 - 22)	10 (7 - 26)	10 (5 - 14)	0.82	0.37	0.02
Lymphomonocyte, %	97 (91 - 100)	96 (68 - 98)	74 (39 - 89)	0.73	0.001	<0.001
Glucose (mg/dL)	57 (52 - 64)	56 (46 - 68)	32 (18 - 44)	0.52	0.04	<0.001
CSF/serum glucose ratio	0.50 (0.45 - 0.53)	0.47 (0.36 - 0.51)	0.21 (0.15 - 0.33) (n=22)	0.07	0.001	<0.001
Protein (mg/dL)	85 (58 - 127)	128 (100 - 210)	202 (129 - 322)	0.001	0.20	<0.001
ADA (U/L)	3.4 (1.7 - 6.0) (n=60)	7.7 (4.8 - 13.0)	13.3 (9.2 - 20.8) (n=21)	<0.001	0.003	<0.001
Highest ADA (U/L)	3.6 (1.7 - 6.4) (n=60)	12.1 (8.0 - 15.0)	16.6 (11.7 - 31.6) (n=23)	<0.001	0.03	<0.001
Course of illness						
ICU hospitalization, n (%)	4 (6)	4 (25)	10 (42)	0.049	0.28	<0.001
Assisted ventilation, n (%)	1 (2)	2 (13)	6 (25)	0.10	0.44	<0.001
Outcome, n (%)						
Neurologic sequelae at discharge	11 (18)	6 (38)	10 (46) (n=22)	0.09	0.62	0.007

홍선인, 김성한 등. Unpublished data



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- G/W 2
- CSF e
 - W 32
 - Glu 2
 - M. T
 - Virus
- MRI- o
 - especi
 - sylvian

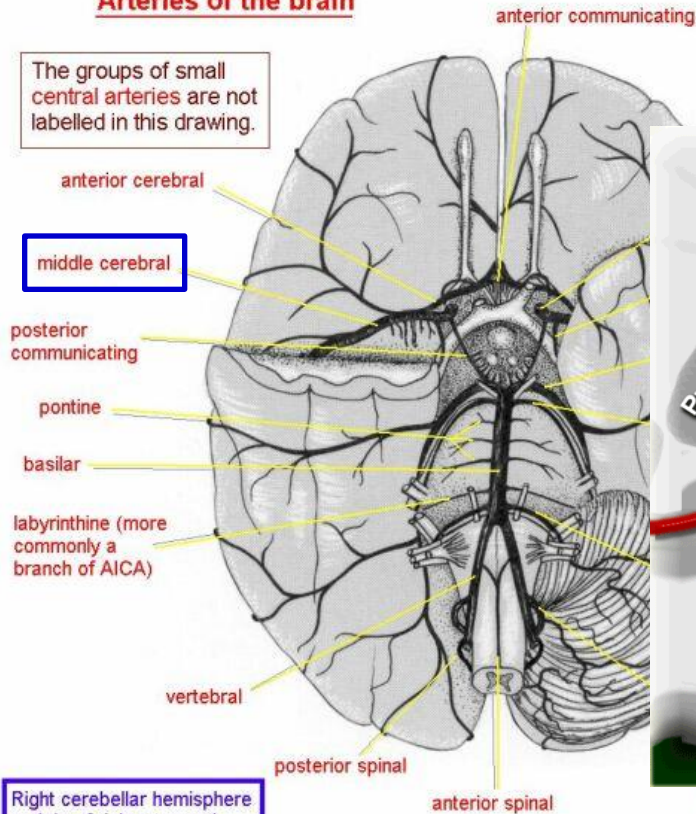
51 year-old Female

- F/U CSF exam
 - W 320 → 15 (1 wk) → 5 (3 wk) → 90 (4 wk) → 800 (6 wk)
 - Protein 318 → 188 (1 wk) → 1644 (3 wk) → 2818 (4 wk) → 3158 (6 wk)
 - ADA 14 → 12 (1 wk) → 84 (3 wk) → 117 (4 wk) → 110 (6 wk)
 - *M. TB* PCR (+) AFB smear (-) → culture (+) and all susceptible *M. tuberculosis*

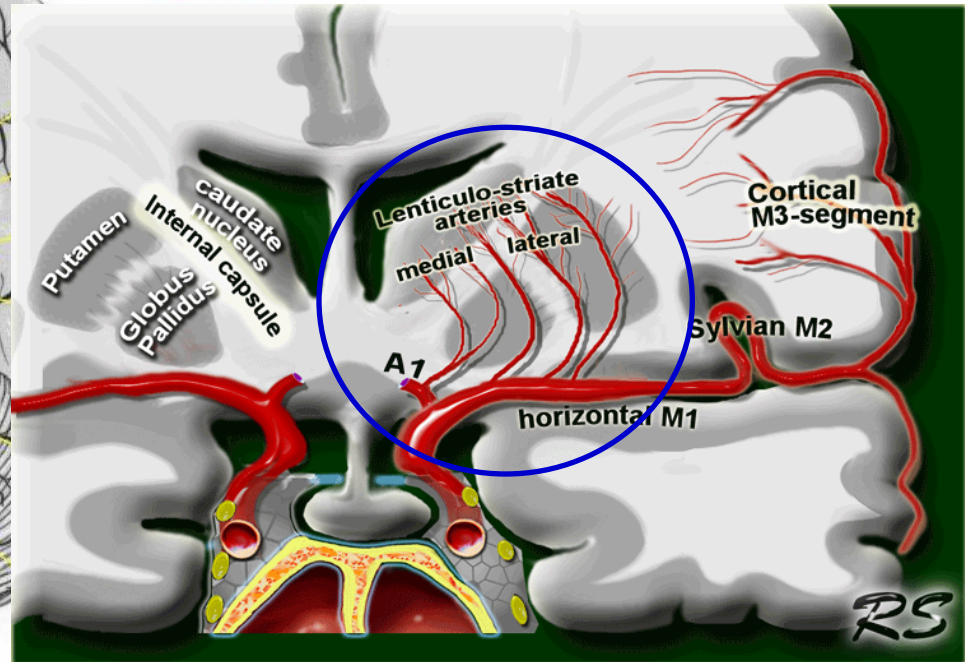


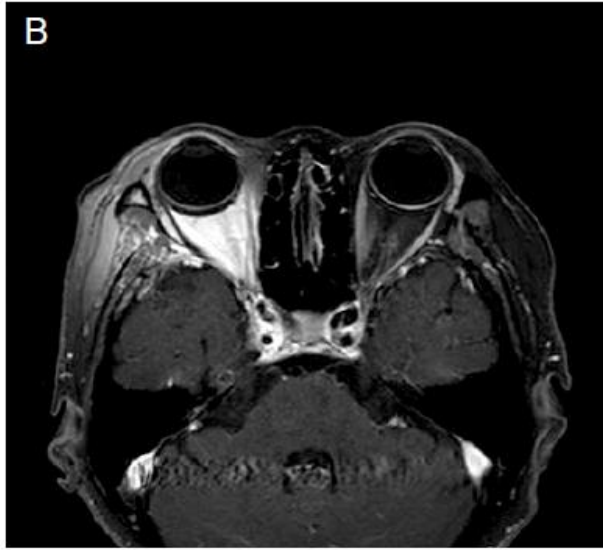
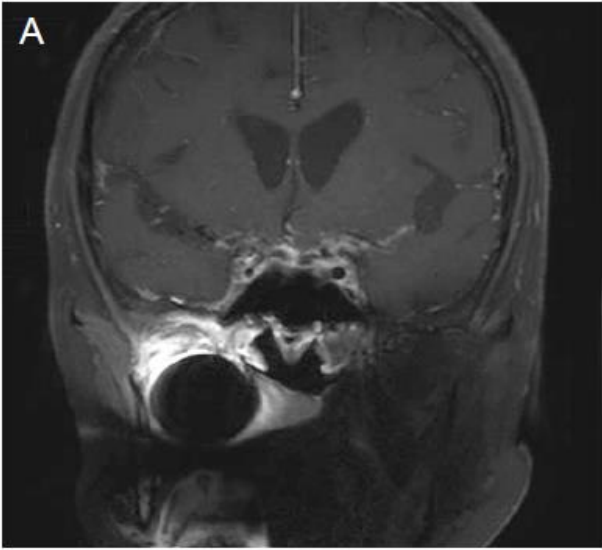
Arteries of the brain

The groups of small central arteries are not labelled in this drawing.

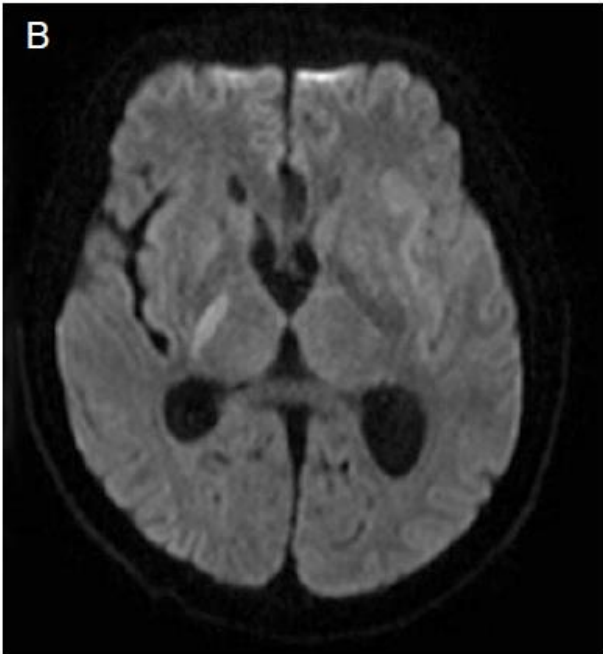
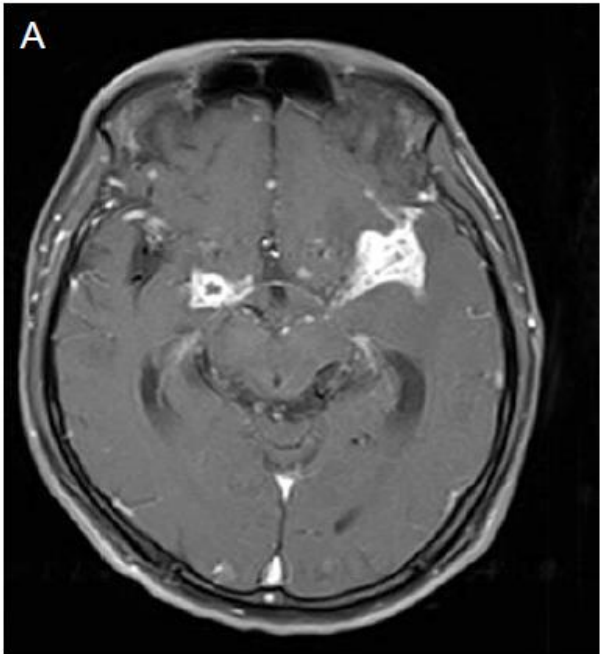


Right cerebellar hemisphere and tip of right temporal lobe have been removed.

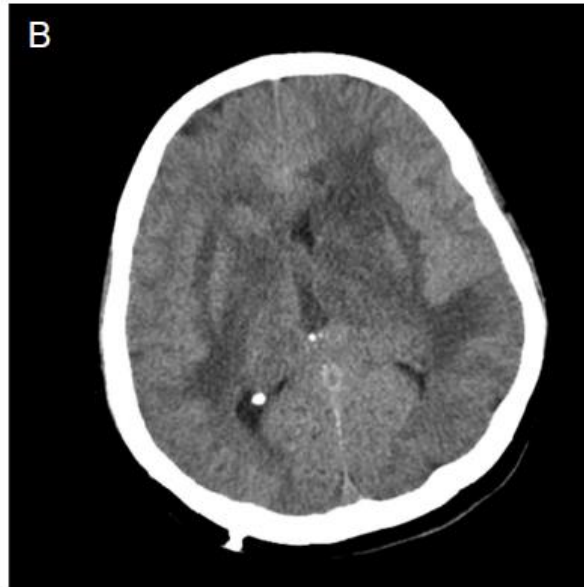
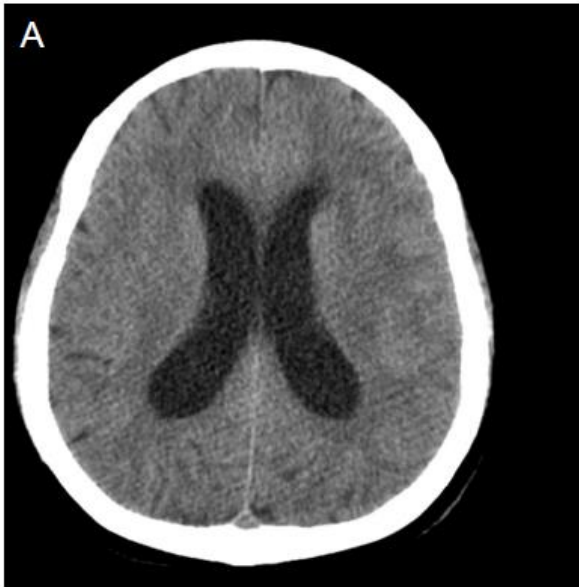




Base cerebral exudate type

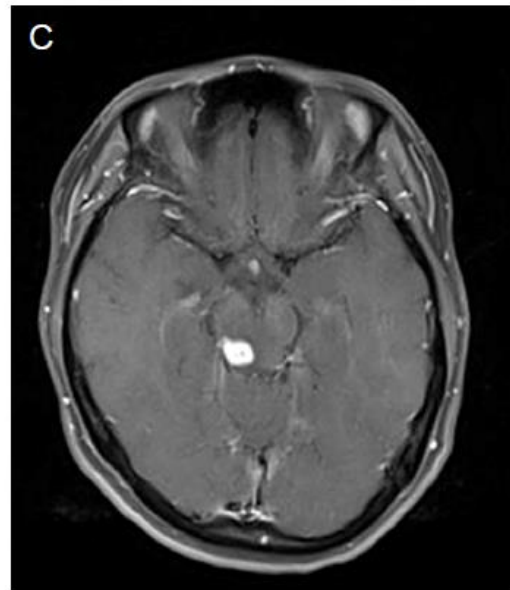
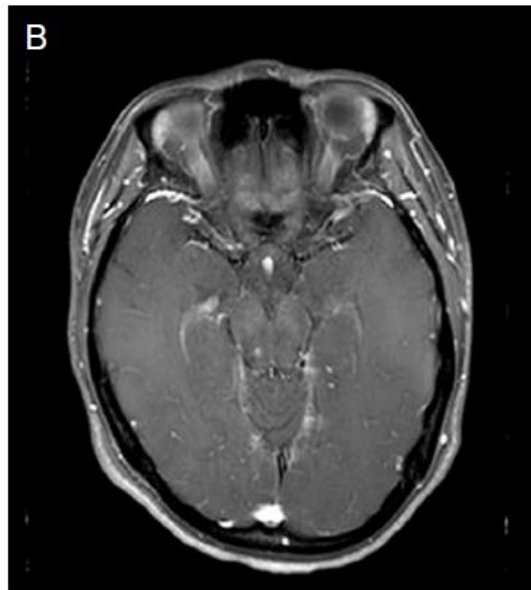


Cerebral vasculitis and infarction type



Hydrocephalus type

Granuloma type



IGRA in E-TB diagnosis

	Sensitivity % (<i>n</i> / <i>N</i> , ^a 95% CI)	Specificity % (<i>n</i> / <i>N</i> , ^b 95% CI)
Confirmed or probable tuberculosis (<i>n</i> = 153) versus not tuberculosis (<i>n</i> = 172)		
Site of infection	84 (129/153, 78–89)	51 (87/172, 43–58)
Lymph node	89 (48/54, 78–95)	60 (6/10, 31–83)
Abdominal	79 (30/38, 64–89)	54 (15/28, 36–70)
Central nervous system	74 (26/35, 58–86)	46 (40/87, 36–56)
Osteoarticular	100 (28/28, 88–100)	55 (21/38, 40–70)
Miliary	89 (25/28, 73–96)	not applicable
Disseminated	88 (42/48, 75–94)	67 (2/3, 21–94)
Presentation		
Chronic forms	93 (52/56, 83–97)	57 (26/46, 42–70)
Indeterminate forms	80 (33/41, 66–90)	54 (21/39, 39–68)
Acute forms	79 (44/56, 66–87)	46 (40/87, 36–56)

IGRA in military TB diagnosis

- 44 patients with military TB^a
- Sensitivity of QFT-GIT 68%^a

Diagnostic Tool	No./Total (Sensitivity %, [95% Confidence Interval])		
	Total (n = 101)	Military TB (n = 52)	Non-military TB (n = 49)
Positive tuberculin skin test	28/64 (44 [32–56])	8/32 (25 [13–42])	20/32 (63 [45–77])
Positive QuantiFERON-TB In-Tube	39/58 (67 [54–78]) [†]	18/27 (67 [48–81]) [‡]	21/31 (68 [50–81]) [§]
Positive T-SPOT.TB	91/101 (90 [83–95]) [†]	47/52 (90 [79–96]) [‡]	44/49 (90 [78–96]) [§]

^aKim CH, et al. *Clin Infect Dis* 2014; 58:986-9
유시내, 김성한. *Medicine* 2015; 94:1-5

질문

- 진단은 결핵성 림파선염이 맞는가?
 - 병리조직에서 결핵인데도 AFB (-) MTB PCR (-) 일 수 있는가?
 - 결핵배양 검사는 꼭 필요한가?
 - 추가로 시행했어야 할 검사는?
- 향후 계획은?
 - 항결핵제 유지 또는 교체?