대한 결핵 및 호흡기 학회
심포지엄

2013. 5. 27

순천향대학교병원
호흡기알레르기내과

Case # 1

50/M

C.C: Evaluation of abnormal CBC

onset) 5일 전

Present illness

- 50세 남자는 내원 12일 전부터 발생한 발열, 오한, 기침, 근육통이 있었음. 내원 10일전부터 증상이 악화됨.
- 내원 5일전 타병원 내원하여 단순흉부사진에서 이상이 있어 내원 1일전까지 폐렴에 대한 항균제 치료를 받고 증상은 호전되었음.
- 그러나 항균제 치료후에도 단순흉부사진에서 병변이 지속되고 말초혈액검사에서 호산구증가증이 지속되어 전원.

Past history

- DM (+) metformin, glyburide
- Hypertension (–)
- Hyperlipidemia (+) fenofibrate, femfibrozil, omega3
- TB (–), Allergies (–), Hepatitis (–)
- Social history
  - Alcohol drinking(–)
  - Cigarette smoking(+) 60 PY, 8년전 금연
  - Engaged in transportation
  - Living in LA, USA 내원 12일전 귀국
- OP & hospitalization Hx. (–)

Review of system I

1. General

General weakness (-)

Fever (+)

Sweating (-)

Fatigue (-)

Chill (+)

Weight change (-)

2. Chest

Dyspnea (-)

Orthopnea (-)

Cough (+)

Sputum (-)

Chest pain (-)

Hemoptysis (-)

Review of system II

3. Abdomen

Loss of appetite(-)

Nausea (-)

Vomiting (-)

Dysphagia (-)

Abdominal pain (-)

4. Genitourinary tract

Hematuria (-)

5. Back & Extremities

Edema (-)

Back pain (-)

Physical examination I

1. Vital sign

BP 130/90mmHg　　PR 100 회/분

BT 36.7 ℃　　RR 20회/분

2. General appearance

Not so ill-looking appearance with alert mental status

Physical examination II

3. HEENT

No pale conjunctivae No dehydrated tongue

No cervical lymph node palpitation

4. Chest

Crackle in RLLF

Normal fremitus

Regular heart beat without murmur

Physical examination III

5. Abdomen

Soft & flat

Normal bowel sound

Tenderness/Rebound tenderness (-/-)

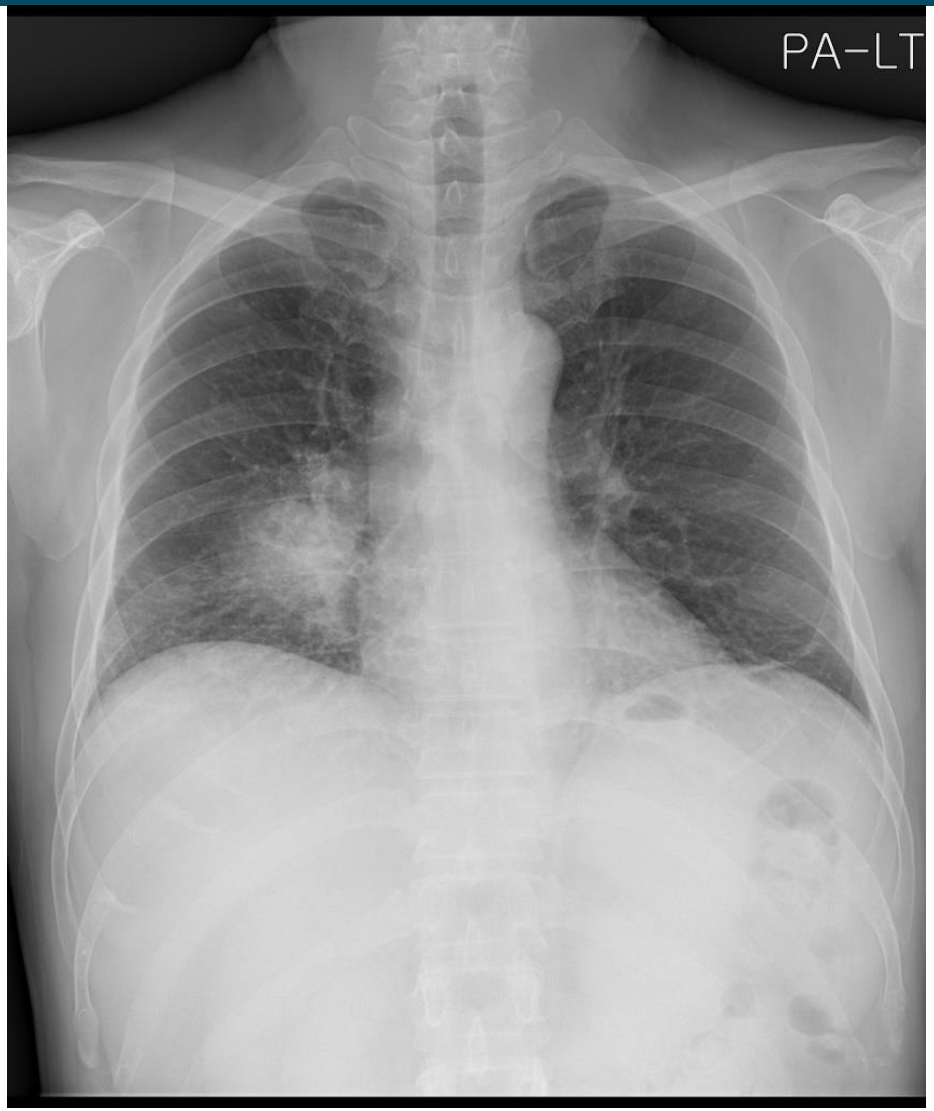
Organomegaly (-)

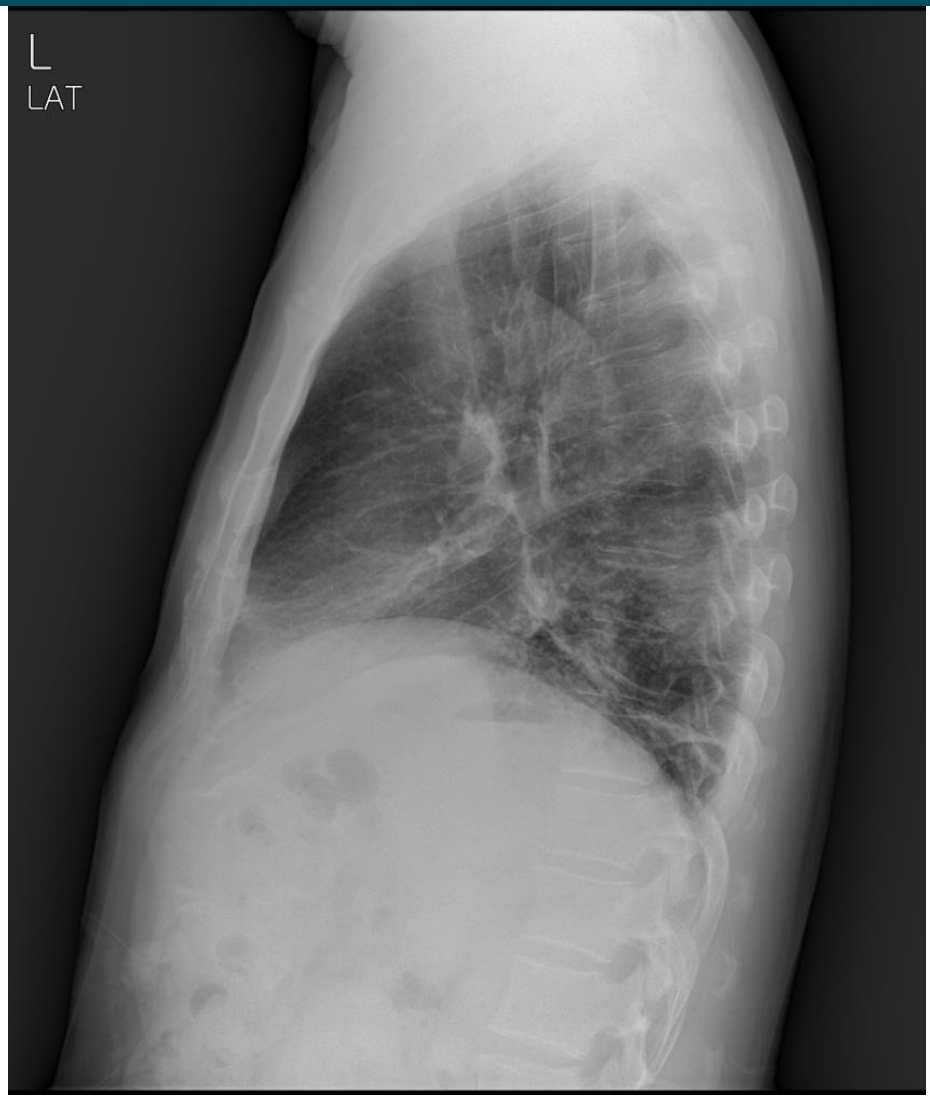
6. Back & Extremities

Pretibial pitting edema (-)

CVA tenderness (-)

Chest x-ray





Laboratory finding

CBC	결과	단위	참고치	내원 5일전
WBC	14.8	10^3/ul	4.0~10.0	15.9
Hemoglobin	14.6	g/dl	13.0~18.0	15.0
Hematocrit	44.3	%	38.0~52.0	42.8
Platelet count	447	10^3/ul	130~400	493

	결과	단위	%	내원 5일전 (%)
Neutrophil count	9.2	10^3/ul	62.1	70.6
Lymphocyte count	1.9	10^3/ul	12.9	12.0
Monocyte count	0.8	10^3/ul	5.2	1.3
Eosinophil count	2.8	10^3/ul	19.0	15.5
Basophil count	0.1	10^3/ul	0.8	0.6

Laboratory finding

Chemistry	결과	단위	참고치
Total protein	7.5	g/dl	5.8~8.1
Albumin	4.7	g/dl	3.1~5.2
AST	23	IU/l	0~40
ALT	17	IU/l	0~40
BUN	12	mg/dl	8.0~20.0
Creatinine	0.93	mg/dl	0.6~1.2
LDH	232	U/L	106~211
Amylase	39	U/L	28~100

Electrolyte	결과	단위	참고치
Sodium	140	mmol/L	135 ~ 153
Potassium	5.1	mmol/L	3.5 ~ 5.3
Chloride	103	mmol/L	99 ~115

Laboratory finding

	결과	단위	참고치
Total cholesterol	186	mg/dl	130~220
Triglyceride	283	mg/dl	0~200
HDL-cholesterol	26	mg/dl	42~67
LDL-cholesterol	111	mg/dl	0~140
HbA1C	7.9	mg/dl	4.1~6.1
hs-CRP	2.77	mg/dl	0.01~0.29
ESR	68	mm/hr	0~20

Problems list

Eosinophilia

Consolidation on Rt. lung

Fever

Impression

Scenario 1
#1 Eosinophilic lung disease
Paragonimiasis
Hypereosinophilic syndrome

Scenario 2
#1 Lung mass
Organizing pneumonia
Malignancy
#2 Eosinophilia
parasite infection, Drug, allergic disease

Diagnostic plan

Chest CT with enhancement

PB morphology

Stool exam for parasite

ELISA test for *P.Westermani*

Total IgE

Radiologic finding

Laboratory finding

ELISA test for Antigen	결과
Cysticercus	negative
P. Wetermani	negative
Sparganum	negative
C. sinensis	negative

	결과
Stool exam for parasite	negative

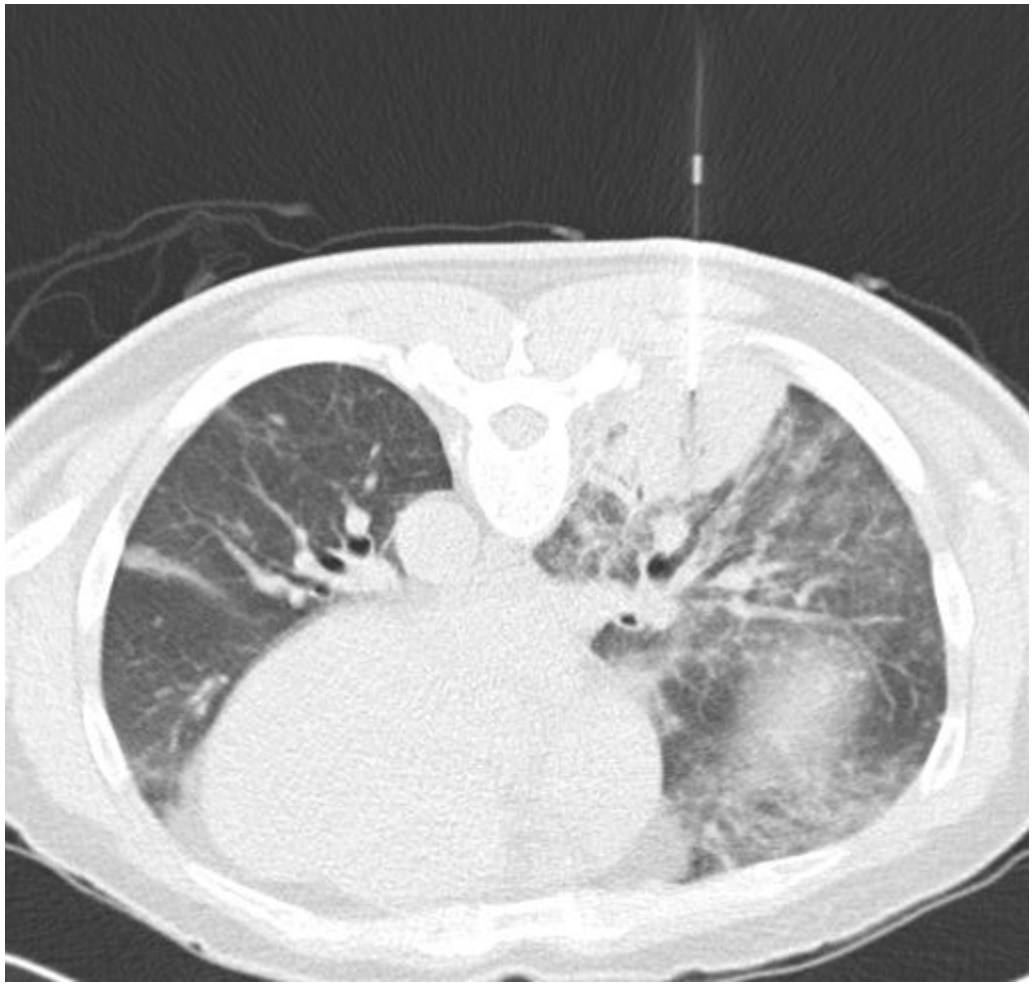
	결과
Sputum Gram stain and culture	No growth
Sputum AFB smear and culture	No growth

	결과
PB morphology	Mild monocytosis, marked eosinophilia(19%)

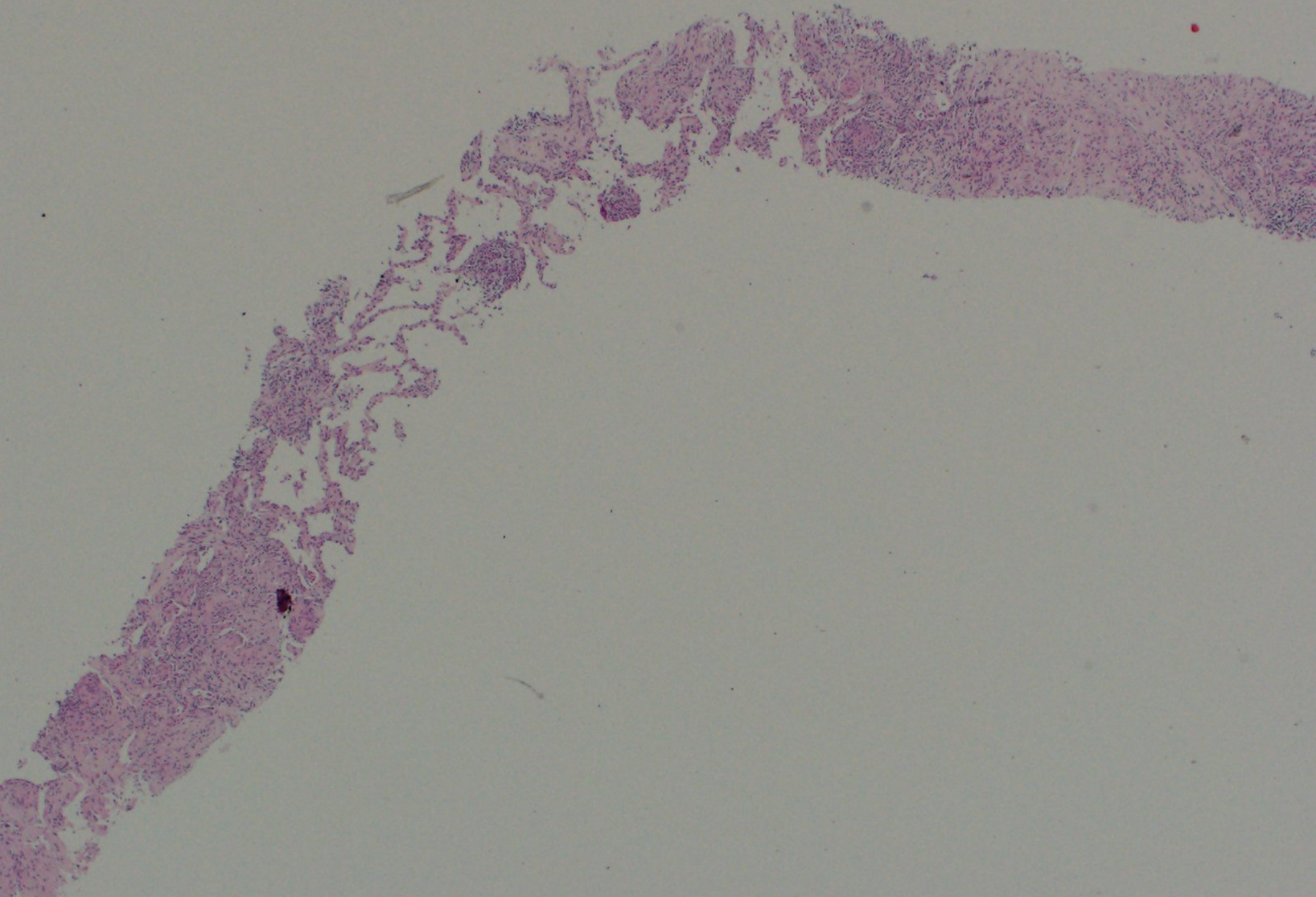
	결과
Total IgE	40.6 kU/L

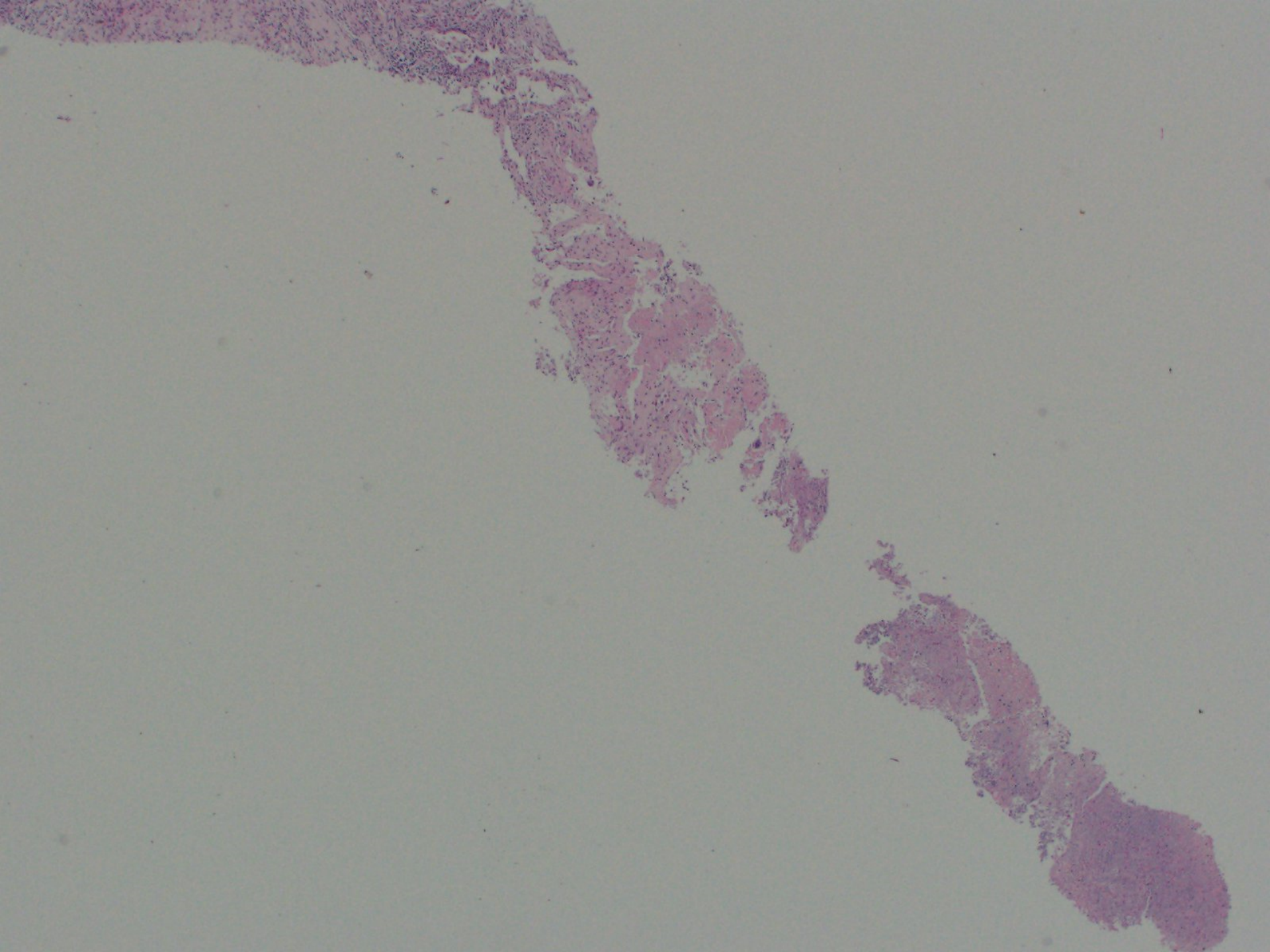
Question & Answer

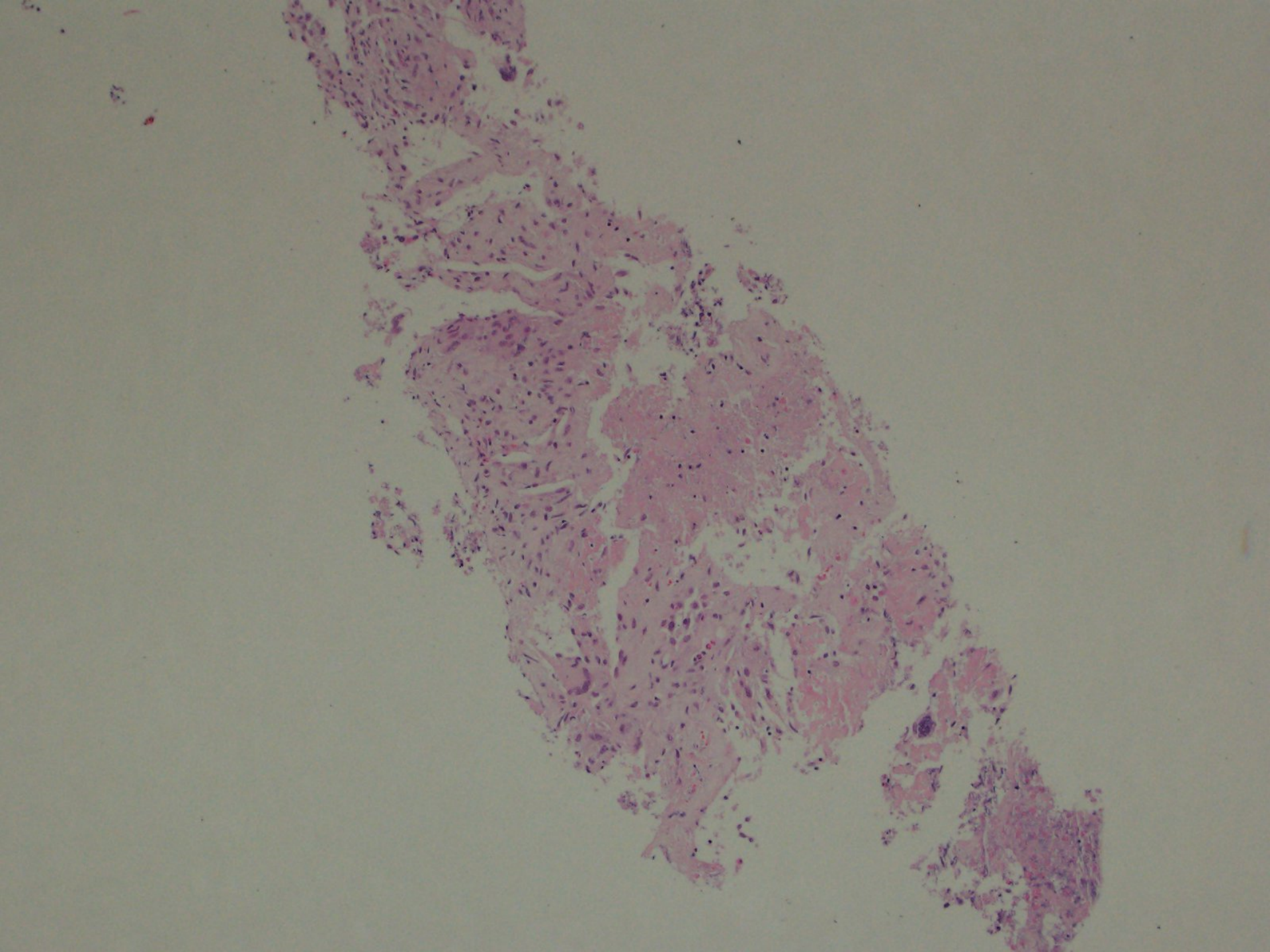
Progress

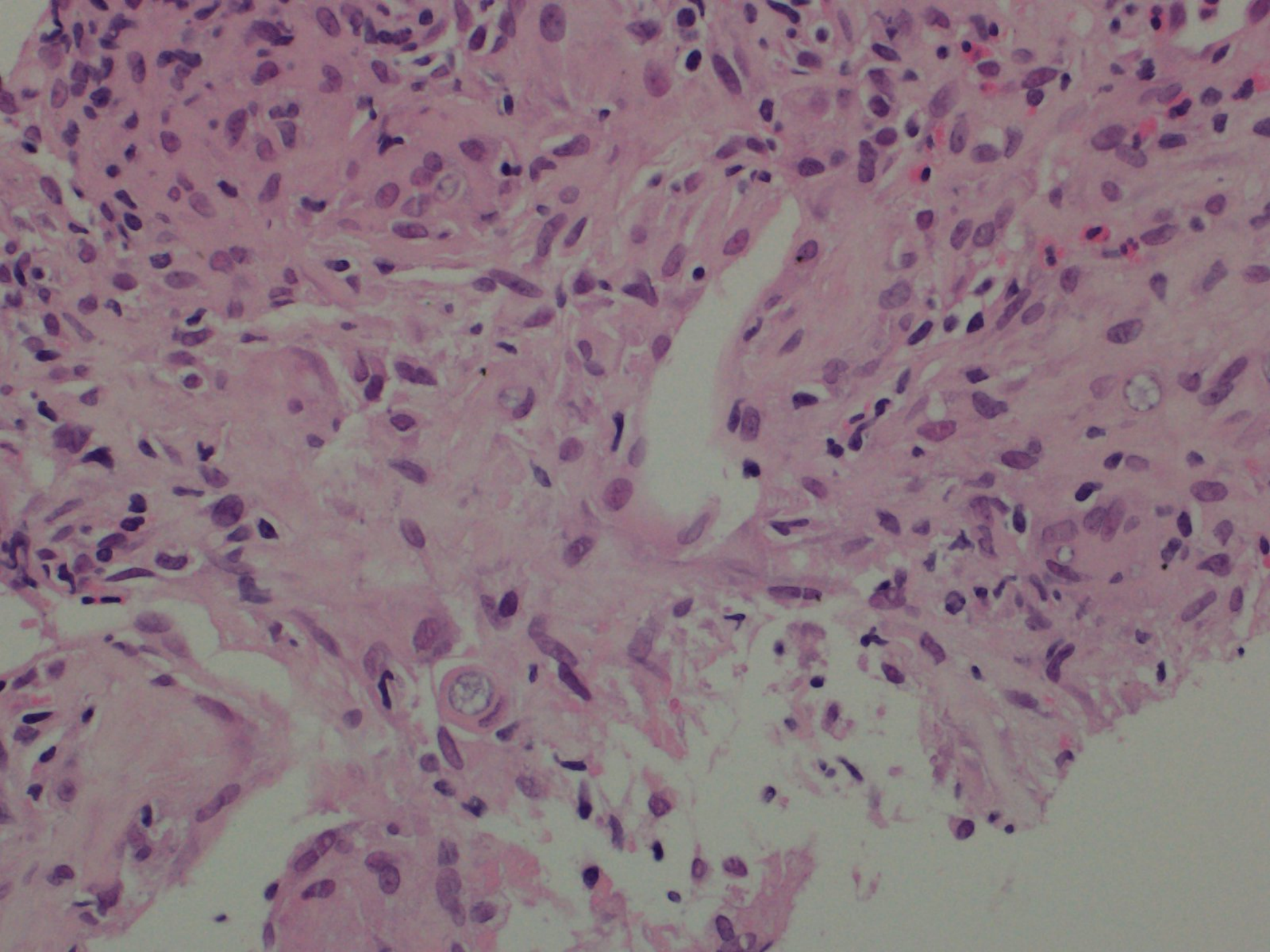


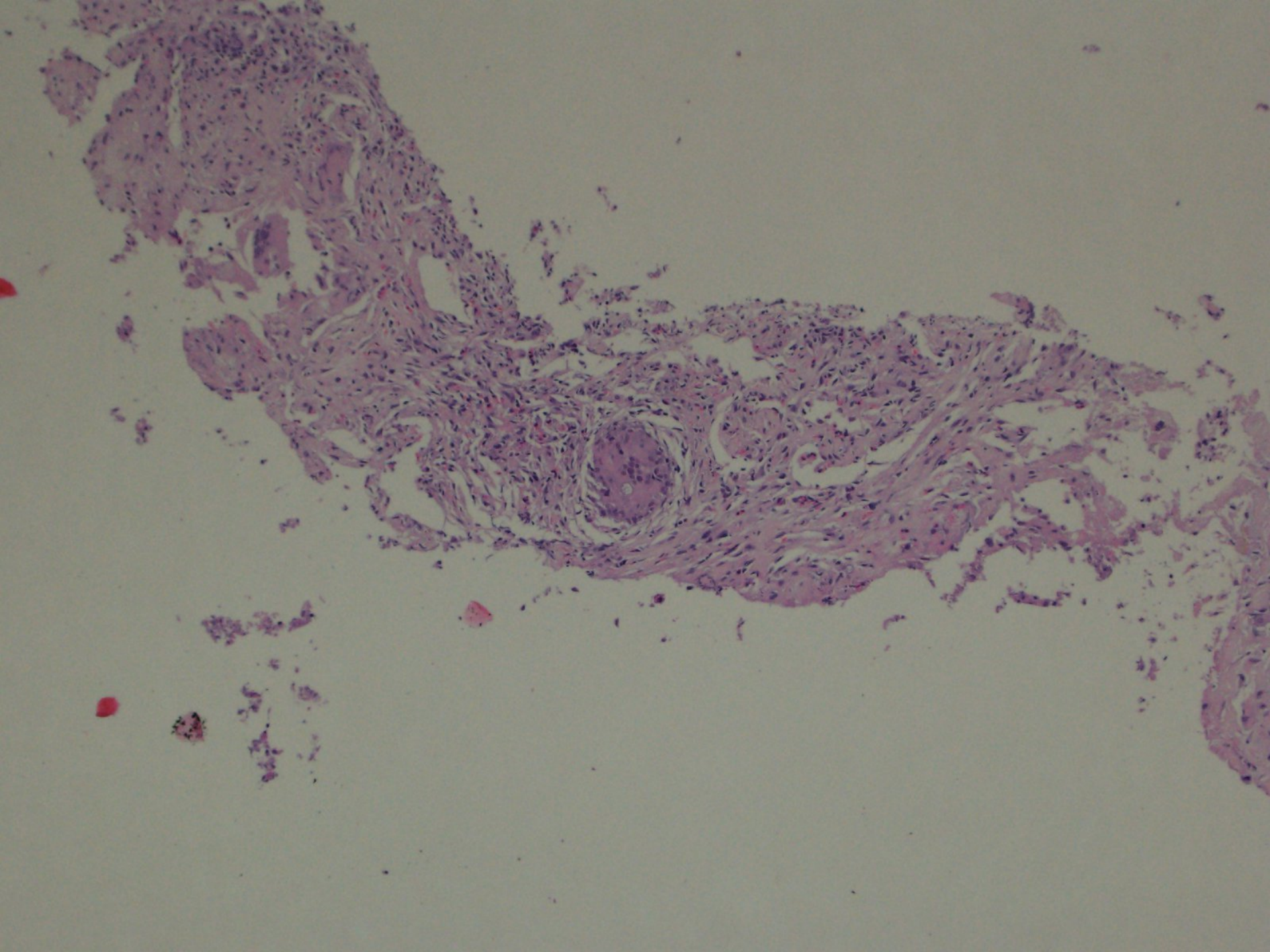
Pathologic findings

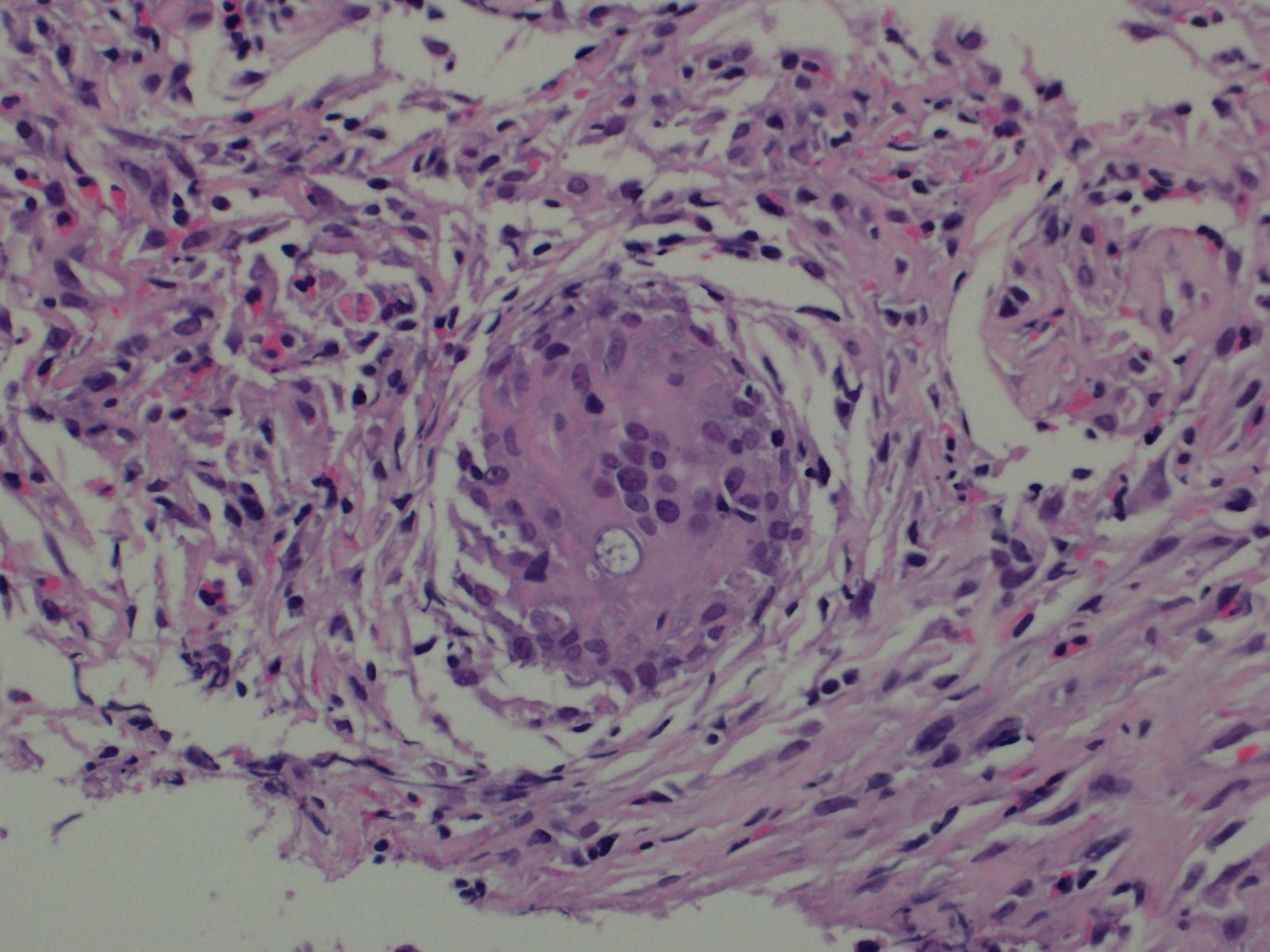


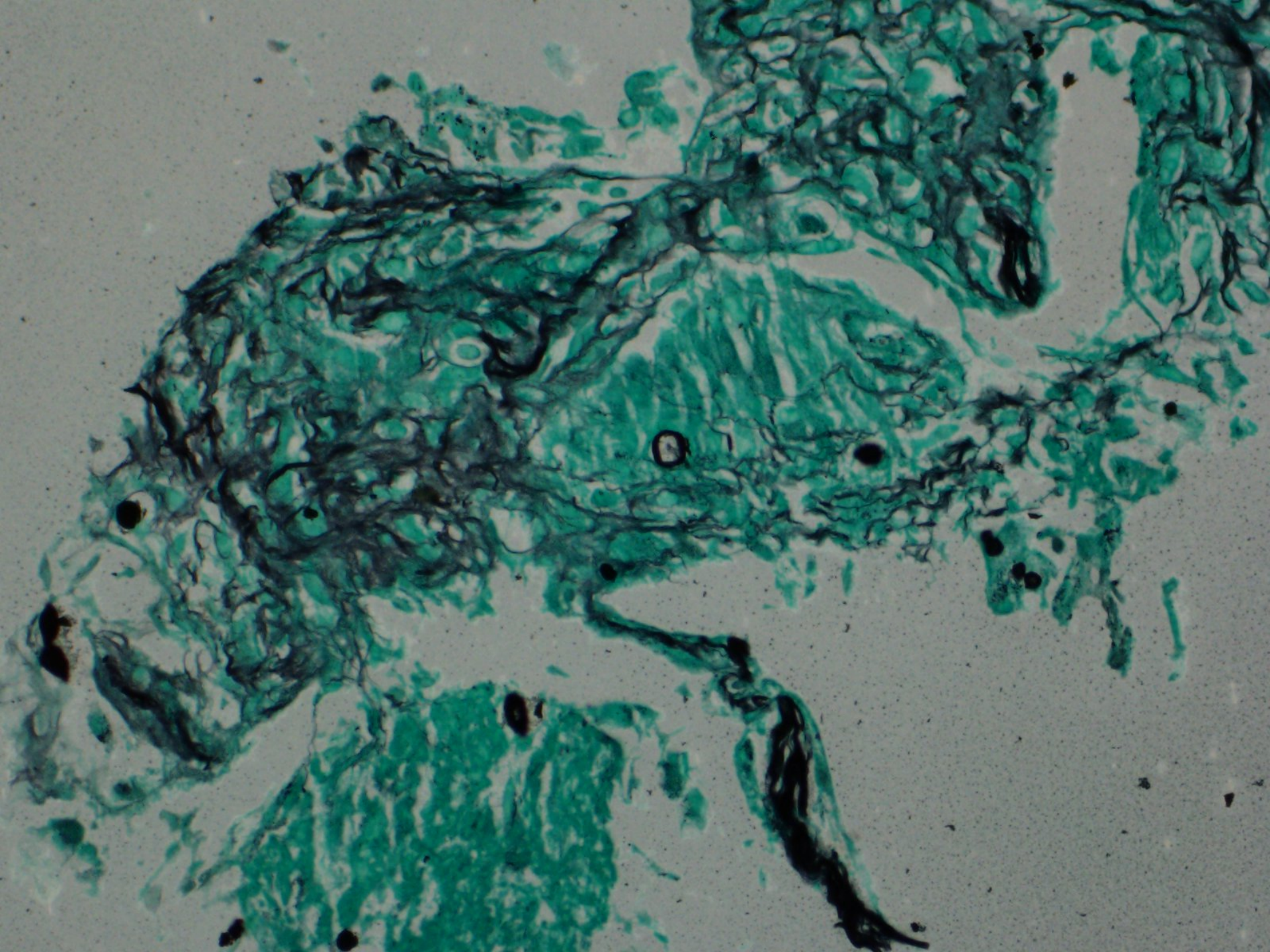


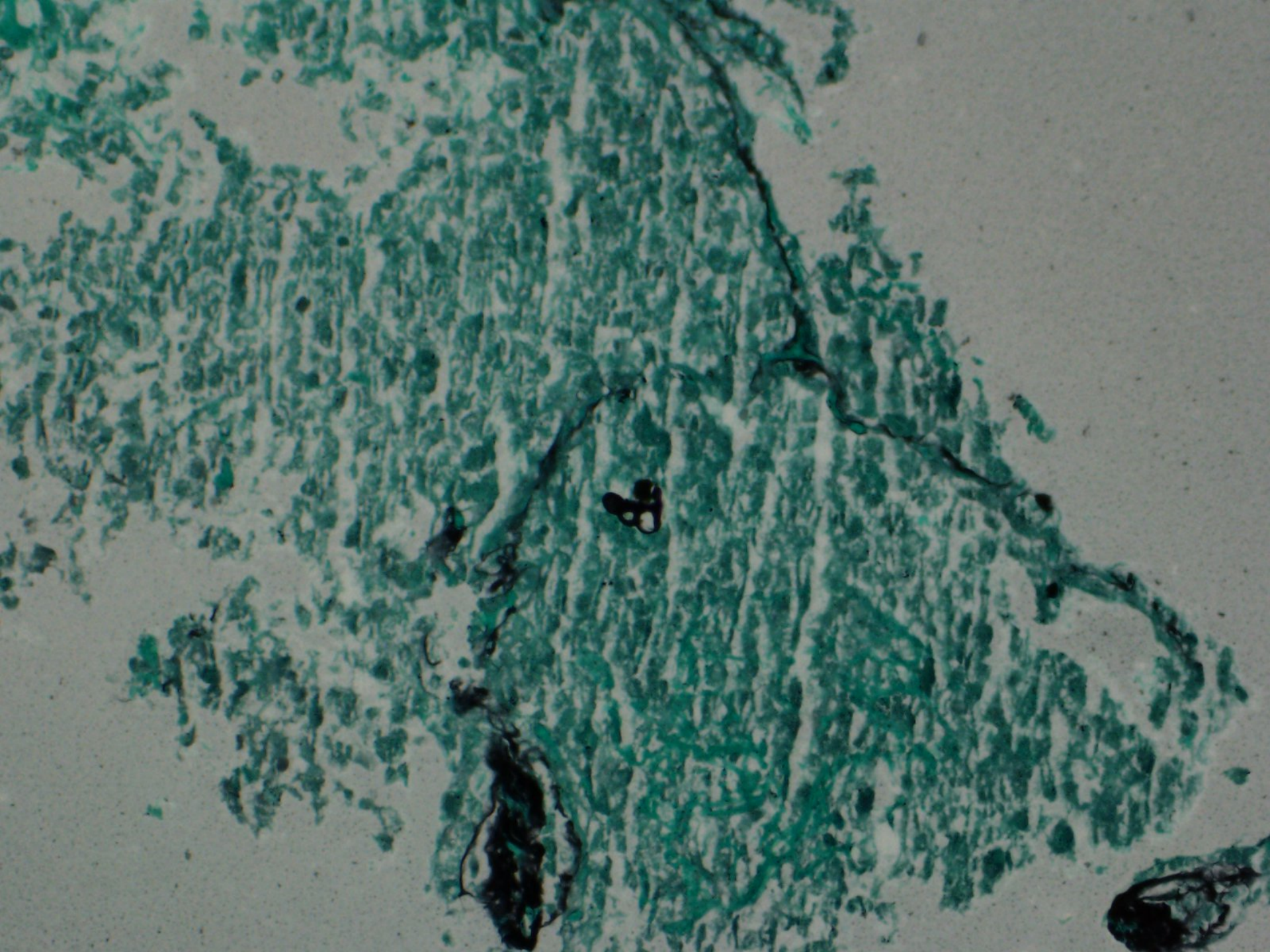


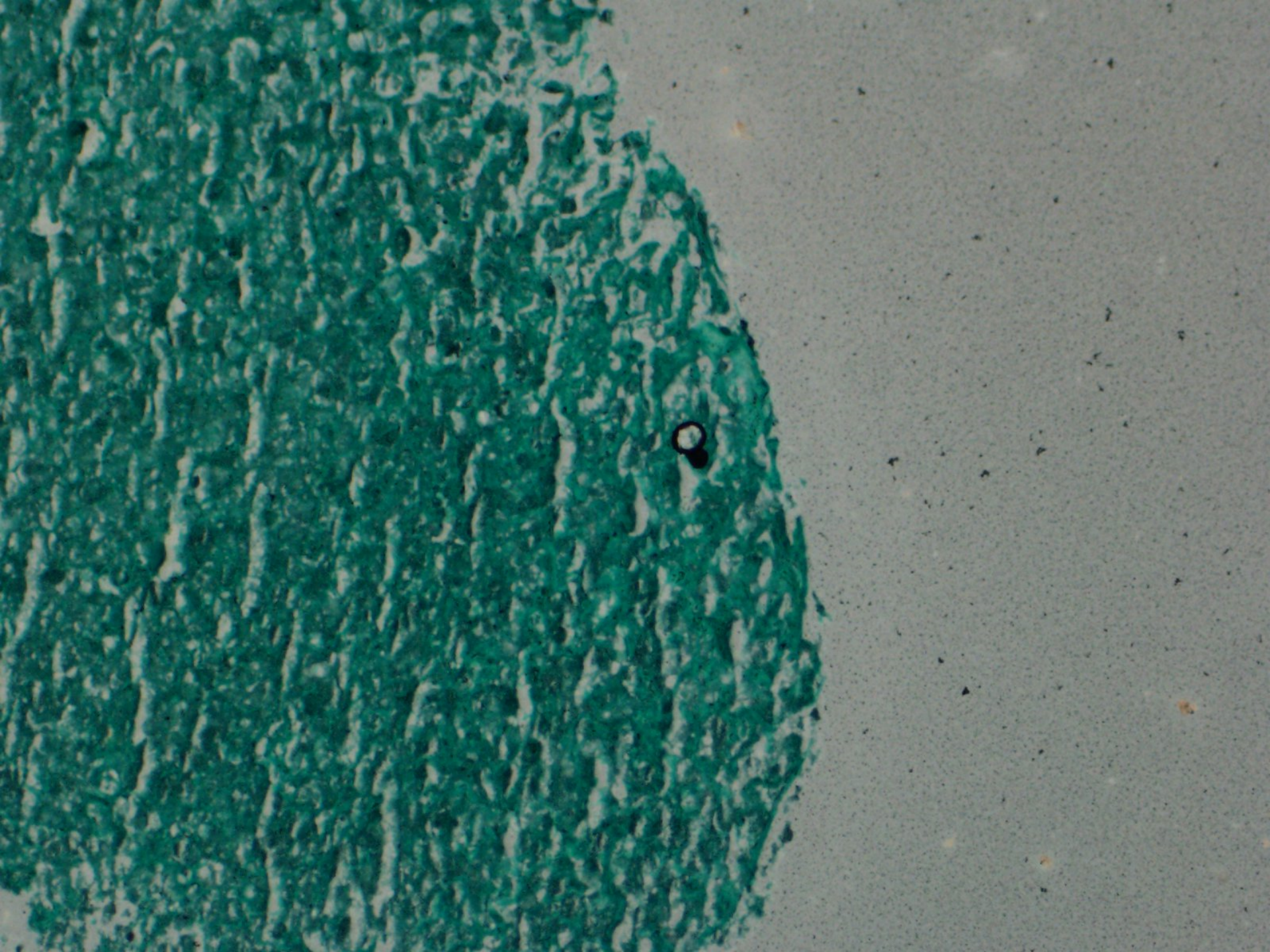


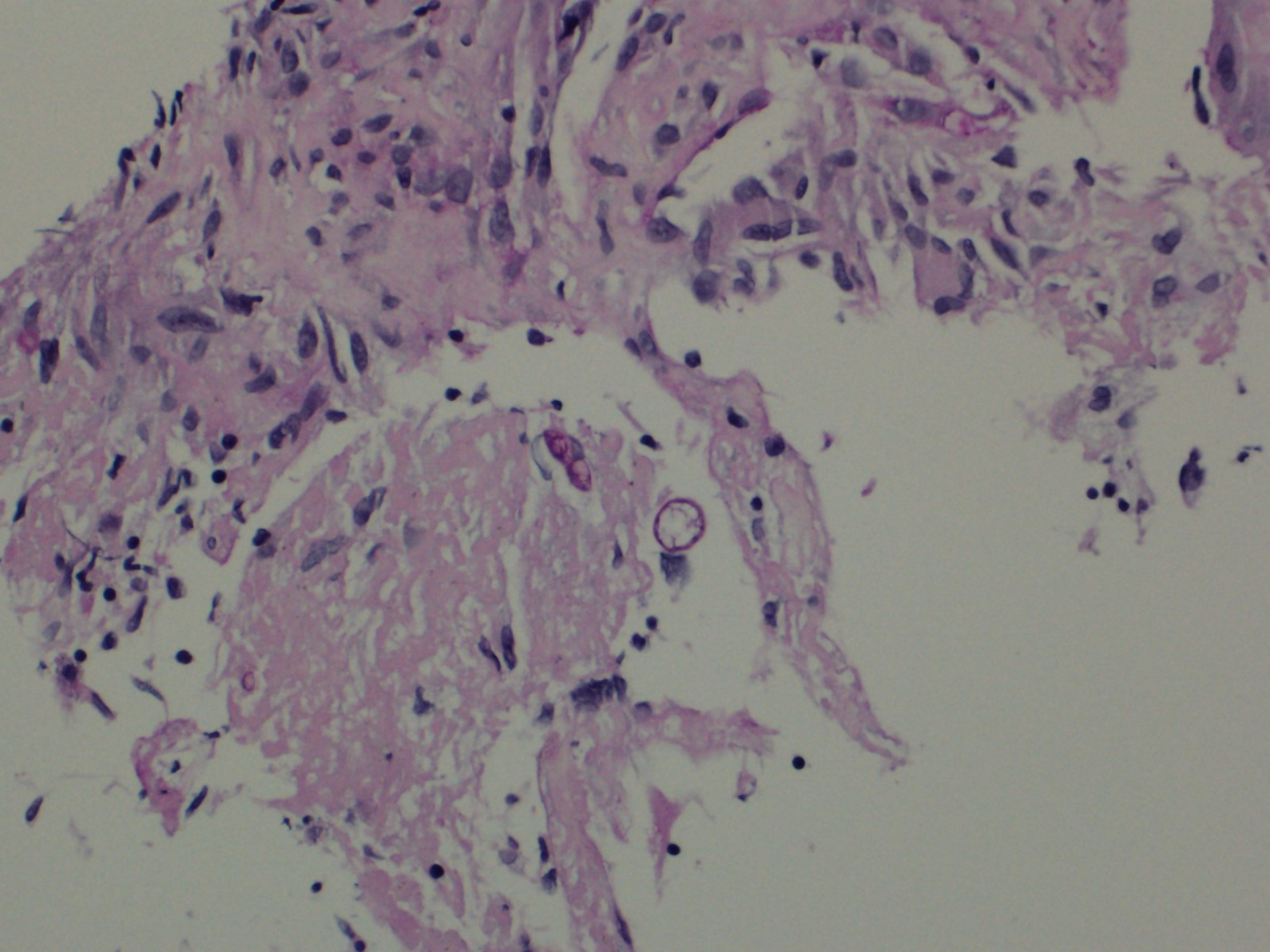


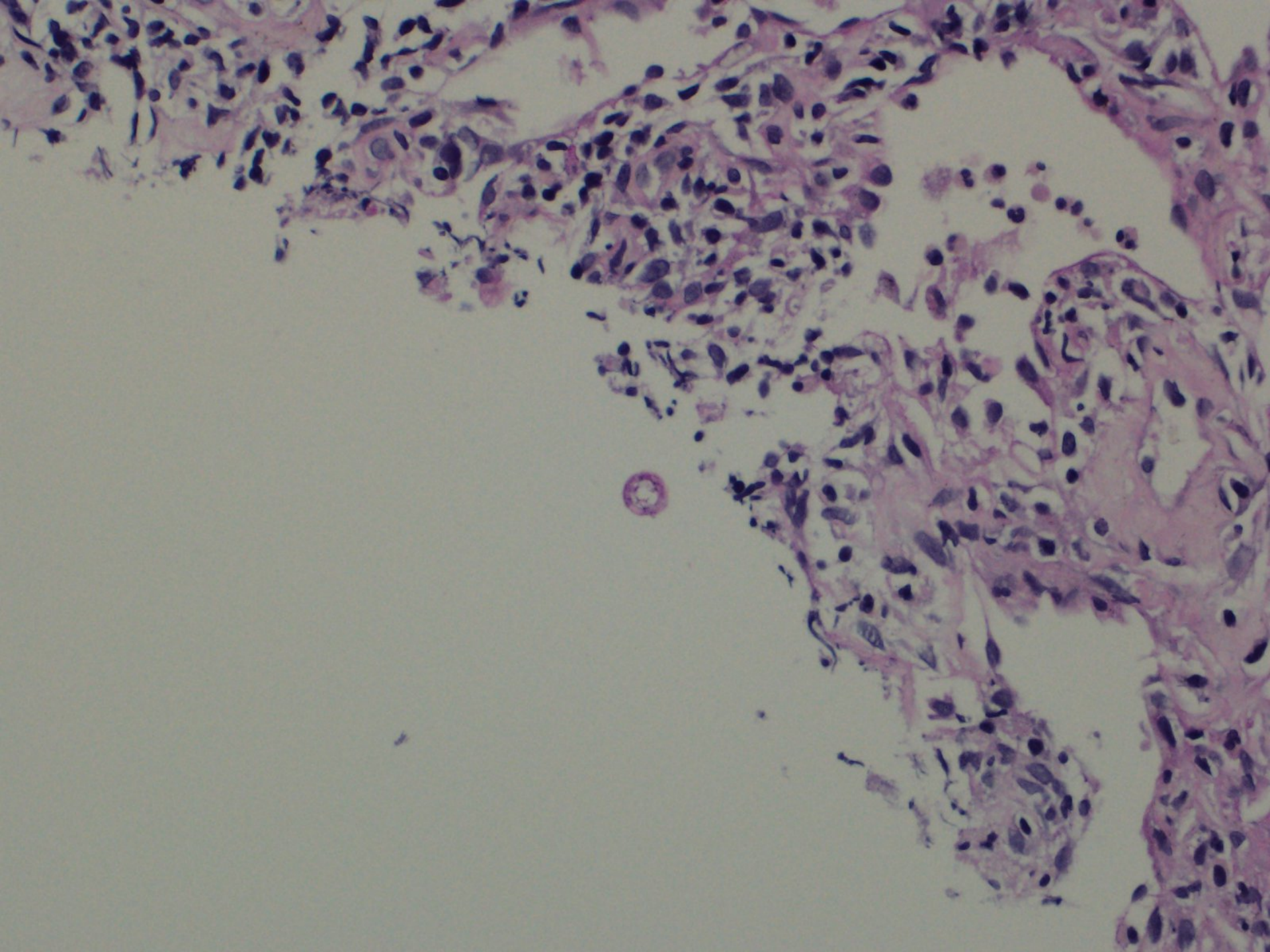












Microbiologic finding

Final Diagnosis

Coccidioidomycosis

Progress

Treatment: Itraconazole 400mg 90days

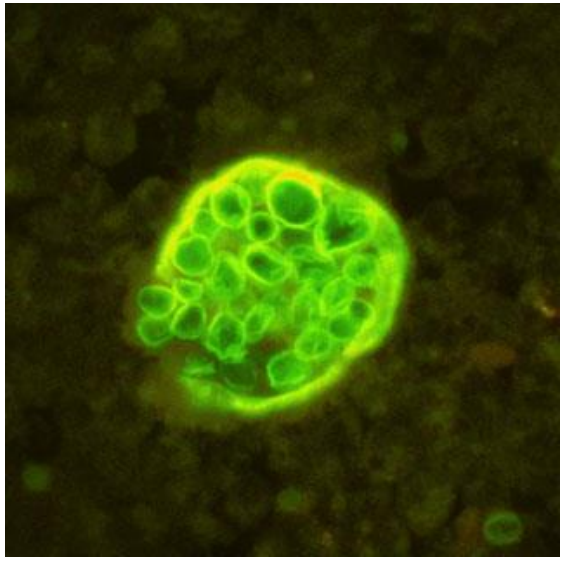
Return to USA

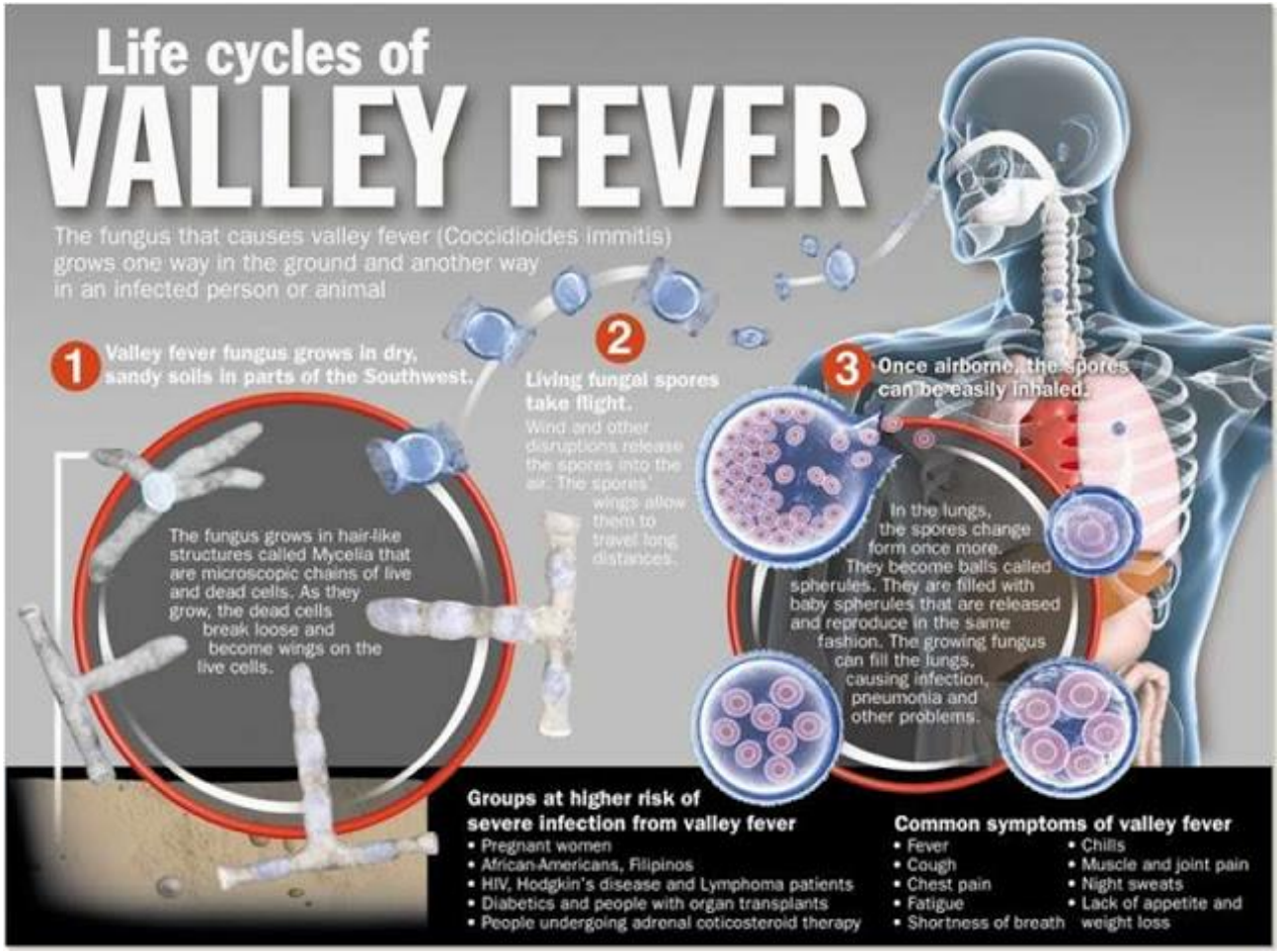
Review

Coccidioidomycosis

Coccidioidomycosis

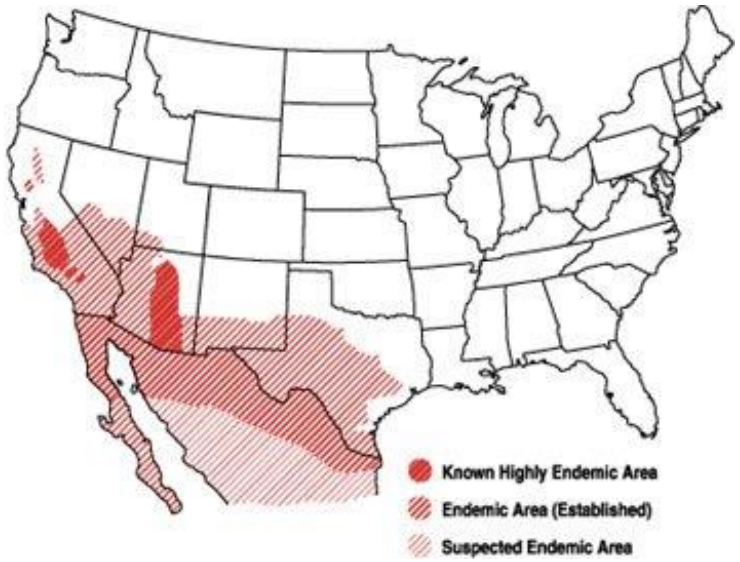
- Also known as valley fever





Coccidioidomycosis

- Results from inhaling the spores of *Coccidioides* species (*Coccidioides immitis or Coccidioides posadasii)*
- The estimated numbers of infections per year ~150,000



southern Arizona, central or other areas of California, southern New Mexico, and west Texas

Clinical Infectious Diseases 2005; 41:1217–23

Coccidioidomycosis

- *Coccidioides* is a fungus found in the soil
- Common cause of pneumonia in endemic areas

  30 – 60% of people in an endemic region are exposed to the fungus at some point during their lives

Centers for diasese control and prevention

Coccidioidomycosis

- The most common clinical presentation :

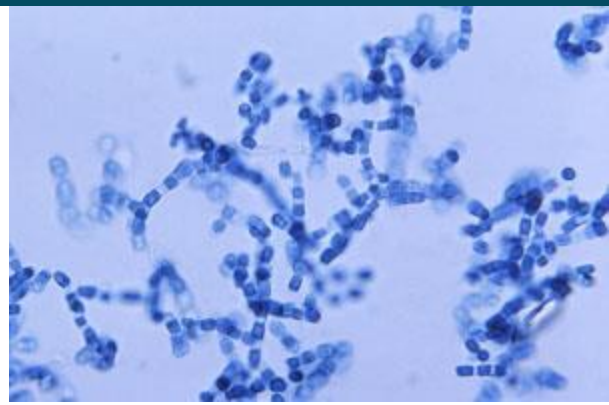
  1–3 weeks after exposure

  self-limited acute or subacute community-acquired pneumonia

- usually indistinguishable from bacterial or other infections without specific laboratory tests

Clinical Infectious Diseases 2005; 41:1217–23

Diagnosis



- Essential first step :

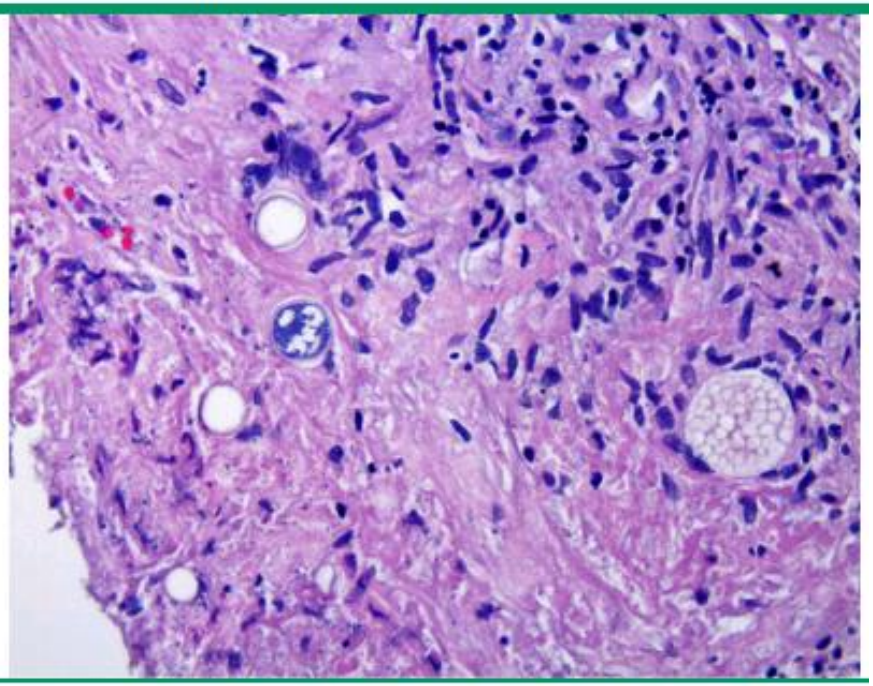
  Considering coccidioidomycosis

  →accurate travel history
- Definitive diagnosis: Isolation of Coccidioides species in culture
- Direct examination of the smear with KOH preparation
- Histopathology: spherules in tissue specimens

  Silver stain : most sensitive
- Outpatients: coccidioidal serologic testing

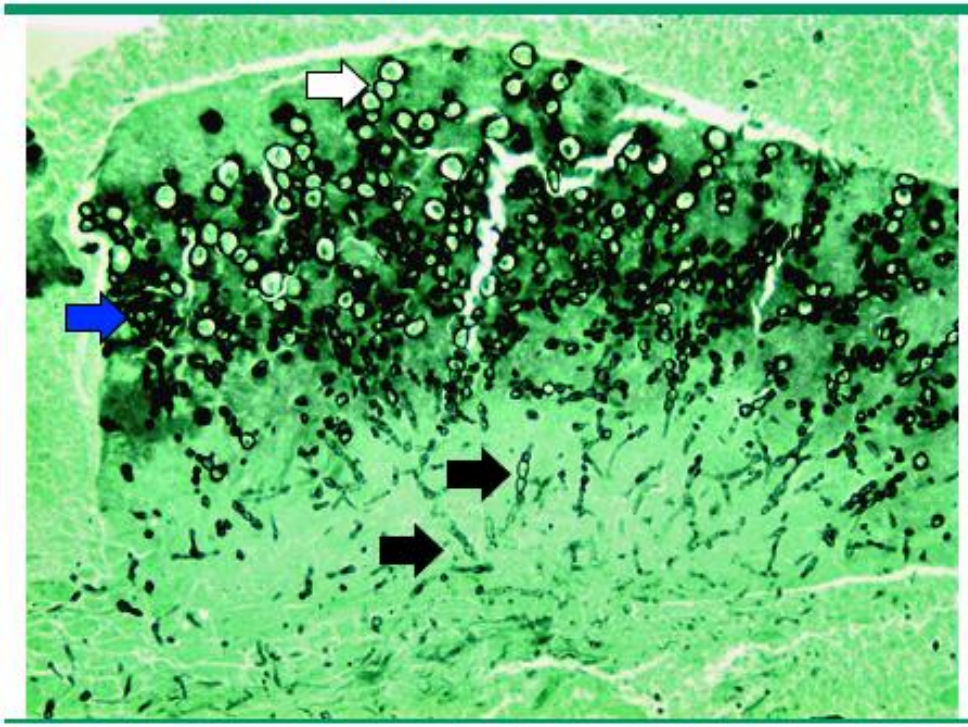
Microbiology

Coccidioides spp in lung tissue



Spherules of Coccidioides spp in a transbronchial biopsy specimen stained with hematoxylin and eosin.

Coccidioides spp in lung tissue



Methenamine silver stain of a pleural biopsy specimen, showing small spherules (white arrow), clumps of endospores (blue arrow), and hyphal forms (black arrows; original magnification, x400).

UpToDate®

Clin Infect Dis 2008;47:823

MANAGEMENT OF Coccidioidomycosis

Defining

- the extent of infection
- identifying host factors that predispose to disease severity

Clinical Infectious Diseases 2005; 41:1217–23

MANAGEMENT OF CLINICAL ENTITIES

- Primary Respiratory Infection
  - *Uncomplicated acute coccidioidal pneumonia*
  - *Diffuse pneumonia*
- Pulmonary Nodule, Asymptomatic
- Pulmonary Cavity
- Chronic Progressive Fibrocavitary Pneumonia
- Disseminated Infection (Extrapulmonary)

Clinical Infectious Diseases 2005; 41:1217–23

MANAGEMENT OF CLINICAL ENTITIES

- Concurrent immunosuppression :

  AIDS, receipt of an organ transplant, high-dose corticosteroids, or inhibitors of TNF (such as etanercept or infleximab)

- Patients who are likely to handle pulmonary coccidioidal infection less well :

  Diabetes mellitus or preexisting cardiopulmonary disease

Clinical Infectious Diseases 2005; 41:1217–23

MANAGEMENT OF CLINICAL ENTITIES

- Healthy patients
  without evidence of extensive coccidioidal infection or risk factors for more serious infection
  → usually do not need antifungal therapy

- Patients with severe illness
  greatly increased risk of dissemination due to immunosuppression or pregnancy
  → should be treated

MANAGEMENT OF Coccidioidomycosis

- Commonly prescribed therapies:
  Oral azole antifungal agents at dosages of 200–400 mg/day
  Recommended treatment courses 3 – 6 months

- *Diffuse pneumonia. Bilateral reticulonodular or miliary:*
  amphotericin B or high-dose fluconazole

- As the patient’ s illness improves,
  continued monitoring at 1–3–month intervals for 1 year or longer

Clinical Infectious Diseases 2005; 41:1217–23

Question & Answer

Case # 2

52/M

C.C: Evaluation of abnormal CBC

onset) 내원 당일

Present illness

- 52 세 남자는 내원 1년 9개월 전 NSCLC(adenocarcinoma, T2bN2M1a) 진단받았음.
- EGFR mutation in exon 21(L858R) 양성이었으나 보험문제로
  Chemotherapy 시행
  paclitaxel (175mg/m^2) + carboplatin (AUC 4) 6 cycles
  gemcitabin (1000 mg/m^2) + vinorelbine (25 mg/m^2) 3 cycles
  내원 11개월 전 부터 Erlotinib 150mg/day 투여 중 intolerable maculopapular rash 발생하여 내원 5개월 전 부터 100mg/day로 복용하다가 현재는 격일로 복용 중임.
- 내원 11개월 전 brain metastasis로 cyberknife 시행
- 내원 5개월 전 WBRT시행 (Total 3000cGy)
- 수개월 전 부터 지속되는 전신쇠약감 외에 새로운 증상은 없었으나 추적 중 혈액검사에서 이상이 있어 입원함.

Past history

- DM (–), Hypertension (–), TB (–)

- Social history
  - Alcohol (–)
  - Former smoker 26 PY, 1년 전 금연
  - Sales-worker

- OP & hospitalization Hx. (–)

Review of system I

1. General

General weakness (+)

Fever (-)

Sweating (-)

Fatigue (+)

Chill (-)

Weight change (-)

2. Chest

Dyspnea (-)

Orthopnea (-)

Cough (-)

Sputum (-)

Chest pain (-)

Hemoptysis (-)

Review of system II

3. Abdomen

Loss of appetite(-)

Nausea (-)

Vomiting (-)

Dysphagia (-)

Abdominal pain (-)

4. Genitourinary tract

Hematuria (-)

5. Back & Extremities

Edema (-)

Back pain (-)

Physical examination I

1. Vital sign

BP 120/70mmHg　　PR 80 회/분

BT 36.5 ℃　　RR 20회/분

2. General appearance

Chronic ill-looking appearance with alert mental status

Physical examination II

3. HEENT

No pale conjunctivae No dehydrated tongue

No cervical lymph node palpitation

4. Chest

Normal breathing sound and fremitus

Regular heart beat without murmur

Physical examination III

5. Abdomen

Soft & flat

Normal bowel sound

Tenderness/Rebound tenderness (-/-)

Organomegaly (-)

6. Back & Extremities

Pretibial pitting edema (-)

CVA tenderness (-)

Problems list

NSCLC (adenocarcinoma)
Brain metastasis

Chemotherapy session
S/p Radiotherapy

Abnormal CBC

Impression

NSCLC (adenocarcinoma)
Brain metastasis

Chemotherapy session
S/p Radiotherapy

Drug-induced cytopenia

Diagnostic plan

- PB morphology
- Chest PA and left lateral

Radiologic findings

Laboratory finding

CBC	결과	단위	참고치
WBC	7.6	10^3/ul	4.0-10.0
Hemoglobin	12.4	g/dl	13.0-18.0
Hematocrit	34.5	%	38.0-52.0
Platelet count	83	10^3/ul	130-400

	결과	단위	%
Neutrophil count	0.5	10^3/ul	6
Lymphocyte count	2.4	10^3/ul	31
Monocyte count	1.0	10^3/ul	13
Eosinophil count	0.0	10^3/ul	0
Basophil count	0.0	10^3/ul	0

Laboratory finding

Chemistry	결과	단위	참고치
Total protein	7.2	g/dl	5.8-8.1
Albumin	4.5	g/dl	3.1-5.2
AST	17	IU/l	0-40
ALT	17	IU/l	0-40
BUN	20	mg/dl	8.0-20.0
Creatinine	0.81	mg/dl	0.6-1.2
LDH	293	U/L	106-211
Electrolyte	**결과**	**단위**	**참고치**
Sodium	142	mmol/L	135 - 153
Potassium	3.6	mmol/L	3.5 - 5.3
Chloride	99	mmol/L	99 -115

PB morphology
Bone marrow aspiration & biopsy

Diagnosis

NSCLC (adenocarcinoma)
Brain metastasis

S/p Chemotherapy
S/p Radiotherapy

Acute myeloid leukemia
with inv(16)(p13.1q22);CBFB-MYH11
Possible Therapy-related leukemia

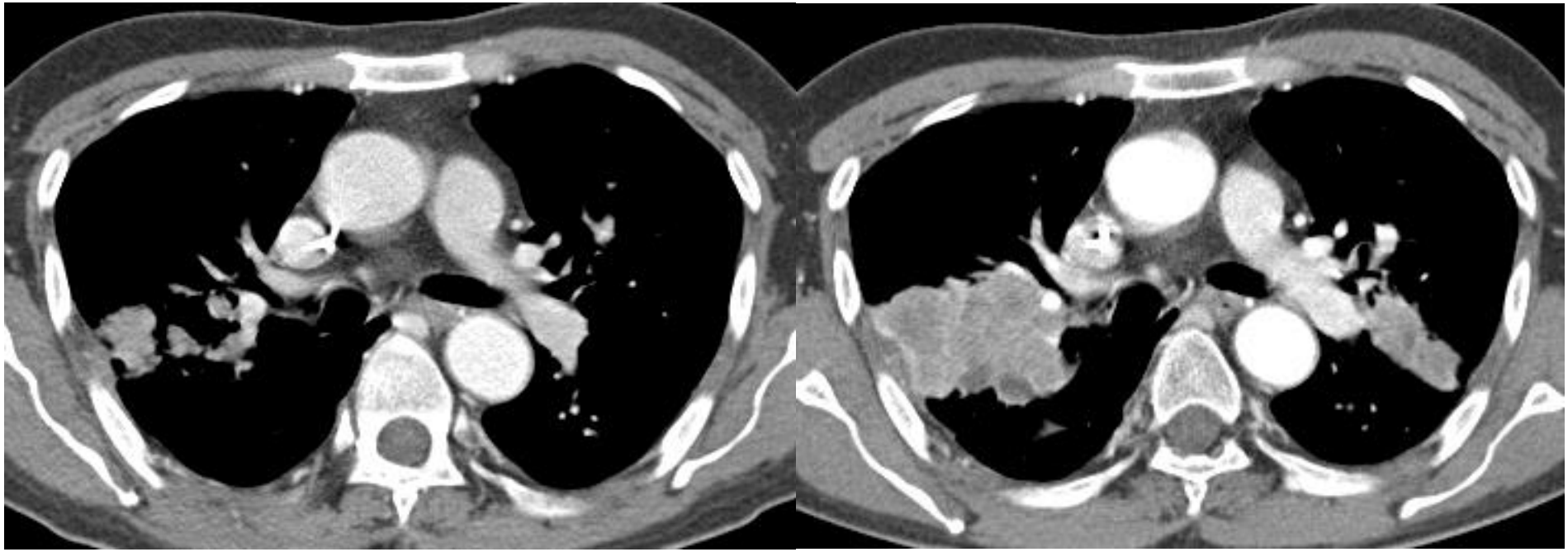
Question & Answer

Progress

Acute myeloid leukemia
with inv(16)(p13.1q22);CBFB-MYH11

Induction chemotherapy [daunorubicin & Cytarabine]
(2012/11/17)
> CR
Consolidation for AML (High dose Cytarabine) (2013/1/4)

Progress



2013/1/5

2013/3/5

Progress

NSCLC (adenocarcinoma)
Brain metastasis

Pemetrexed+cisplatin 2 cycle (2013/3/6–)

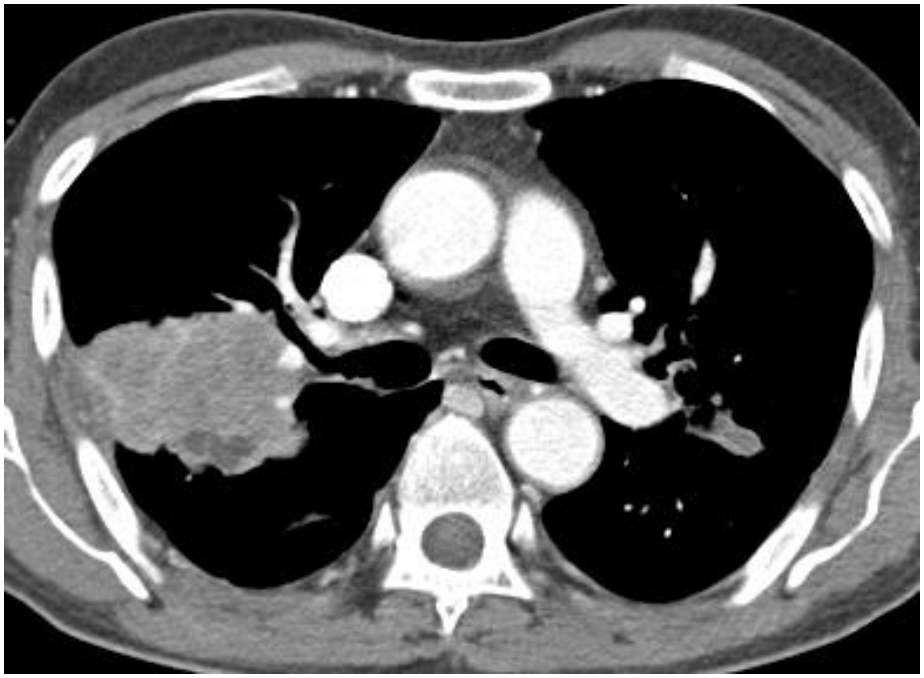
Progress

- 2013/4/18
  prolonged cytopenia after chemotherapy
  CBC 1800-9.6-88k

  BM study: AML in relapse
  Reinduction chemotherapy (2013/4/23)
  (Mitoxantrone & Etoposide)

Progress

2013/3/5



2013/5/21

- Therapy-related leukemia

Previous chemotherapy?

Erlotinib?

- De novo leukemia

Review

Therapy-related leukemia

Therapy-related acute myeloid leukemia

- Therapy-related acute myeloid leukemia (t-AML)
  clinical syndrome occurring as a late complication following cytotoxic therapy

- "therapy-related" leukemia
  based on a patient's history of exposure to cytotoxic agents

- These neoplasms are thought to be the direct consequence of mutational events induced by the prior therapy

Semin Oncol 2008:35:418-429

Classic form of therapy-related leukemia

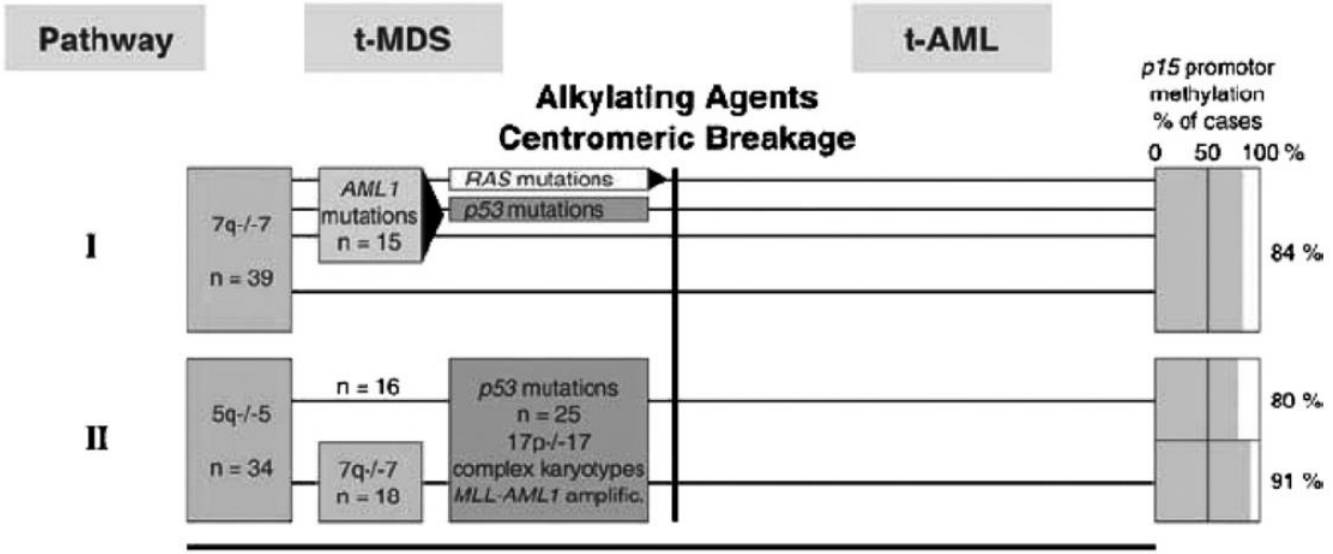
- Alkylating agents and/or radiation therapy
- Degree of dysgranulopoiesis and dysmegakaryocytopoiesis → typically greater

- Characteristic findings:
  Loss of part or all of chromosomes 5 and/or 7
  most common single abnormality:
  monosomy 7 >> del(5q) & monosomy 5

Blood. 2003;102:43-52

Alkylating agents

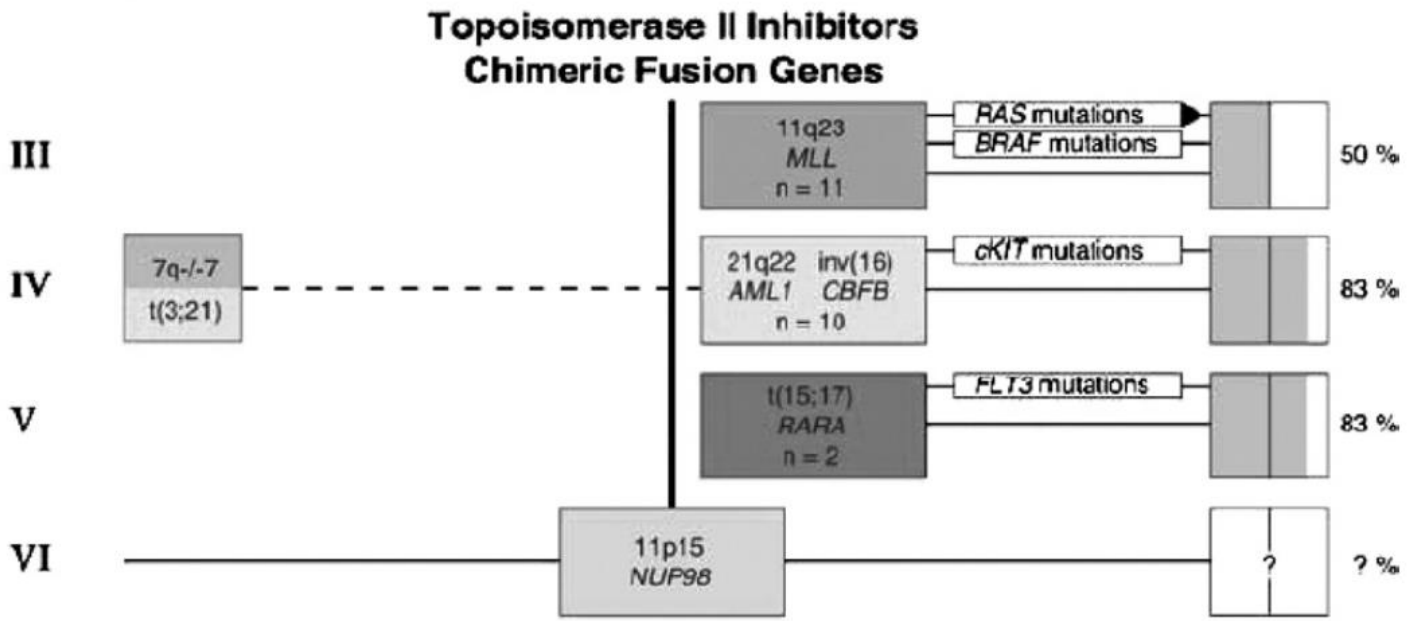
- melphalan, cyclophosphamide
- Dose-response relationship
  between the amount of alkylating agent & the risk of disease development
- Typically occurs within 5 to 7 years after chemotherapy and/or radiotherapy
- Poor prognosis



Leukemia 2006;20:1943-9

Topoisomerase II inhibitors

- Characterized by translocations involving chromosome bands 11q23 or 21q22
- Shorter latency, often within 2 to 3 years
- In some cases, within 12 months



Genes Chromosomes Cancer. 2002;33:413-23

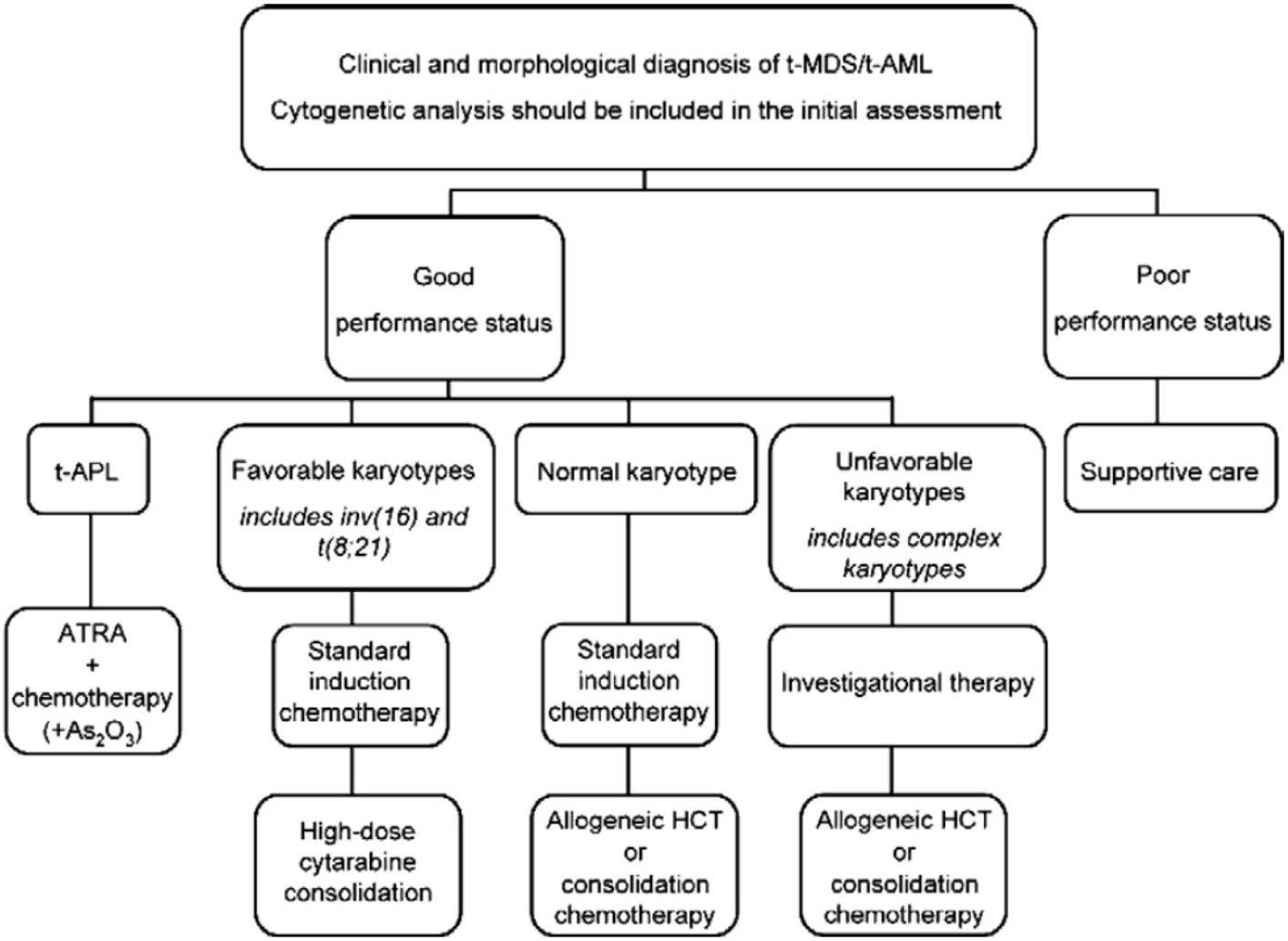
Survival according to cytogenitic group

Karyotype	No. of Patients (%)		Median Survival (mo)		
	t-AML (n = 121)	De Novo AML (n = 1,511)	t-AML	De Novo AML	*P*
Favorable	29 (24)	306 (20)	27	Not reached	.02
Intermediate	34 (28)	903 (60)	12	16	.19
Unfavorable	58 (48)	302 (20)	6	7	.006

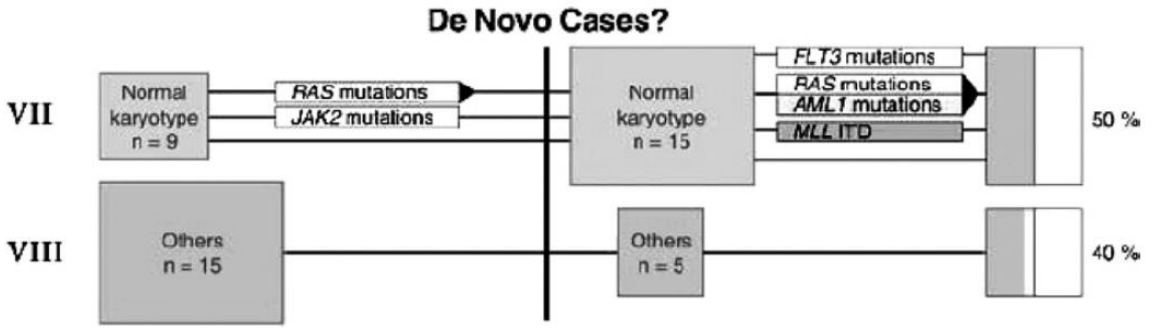
- Almost half of the patients with t-AML (58/121) had an unfavorable karyotype,
- Whereas only about 20% (302/1,511) of the de novo AML patients had an unfavorable karyotype

J Clin Oncol 2001:22:2510-1

TREATMENT OF THERAPYRELATED MYELOID LEUKEMIA



Semin Oncol 2008:35:418-429



- Stochastic event? occurring by chance? or whether certain individuals are at higher risk

- Rapid sequencing of a large number of single nucleotide polymorphisms (SNPs)
  → heritable predisposition to the development of t-AML, such as altered drug metabolism or DNA repair

Semin Oncol 2008:35:418-429

Serious Hematologic Complications Following Erlotinib Treatment

Table I. *Patients with hematologic neoplasias after erlotinib treatment.*

Case	1	2	3	4
Histology	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma	Squamous cell cancer
Duration of erlotinib treatment	4 months	8 months	8.5 months	4.5 months
Blood test results	Grade 4 thrombocytopenia	Leukocytosis	Pancytopenia	Anemia
Time after first-line chemotherapy	11 months	12 months	36 months	14 months
Bone marrow	Low megakaryocytes	BCR-ABL+	23% Myeloblasts	14% Myeloblasts
Diagnosis	MDS	CML	AML	MDS RAEB[a]
Prior treatment	CDDP[b]-Gemcitabine	CDDP-Paclitaxel	VRL[d]-CDDP XRt[e] Carbo-etoposide	Carbo[c]-etoposide

[a]Refractory anemia with excess blasts; [b]cisplatin; [c]carboplatin; [d]vinorelbine; [e]radiation therapy.

- Leukemogenesis may have been due to the previous chemotherapy treatment
- Only etoposide has been related to a second primary malignancy
- Whether or not these hematologic lesions can be attributed to erlotinib treatment is questionable

ANTICANCER RESEARCH 2010:30: 973-976

Leukemogenic effects?

- Gefitinib, another anti-EGFR agent, has been administered for NSCLC and during the treatment, leukemia developed

NEJM 2005:352:842-843

- Paradoxical clinical effects of epidermal growth factor receptor – tyrosine kinase inhibitors for acute myelogenous leukemia

J Clin Oncol 2008:26: 5826-5827

Potential antileukemic effects?

- Erlotinib in a Patient With Acute Myelogenous Leukemia and Concomitant Non–Small–Cell Lung Cancer

J Clin Oncol 2008:26:3645–3646

- Erlotinib antagonizes ATP–binding cassette transporters in acute myeloid leukemia

Cell Cycle 2012:11:4079–4092

Question & Answer