Two cases of Hyper eosinophilia

By
George Ioannidis
Specialist Registrar in Haematology
South East Haematology Training Program

Patient 1

- 55 year old Man
- Initially Presented with a Swelling in His Right Groin in his Late 30s
- History of Dermographism as a teenager

Late 30s

- Elevated white blood cell count
  - Peripheral blood was tested but no bone marrow was taken and no haematology referral was made
  - Enlarged Spleen probably noted at this time
- Lump initially thought to be a hernia was described to Pt as a Cyst after Surgery.

Late 40s

- Sudden onset of painful stiff muscles.
- Significant reduction in mobility
- Required hospital admission
- Splenomegaly confirmed
- Referral to Haematologist (At Halifax)
  - Abnormal blood count noted

- Diagnosed with Hypereosinophilia
- Commenced on Hydroxyurea
- Required antihistamines for recurrent itching.
- Generally stable other than lethargy
  - Explainable by persistent mild Anaemia (9 -10g/dl) which did not require transfusion

Summer 2000

- Significant lethargy – struggling to cope
- Depression
- Commenced on prednisolone
- Subsequently collapsed with salmonella sepsis 2 weeks later.
- Reactive arthritis of left knee was treated with local steroid injection
- Steroids led to hyper-mania which settled after readmission to hospital

October 2002

- Patient noted very tender area above left knee.
- Pain continued

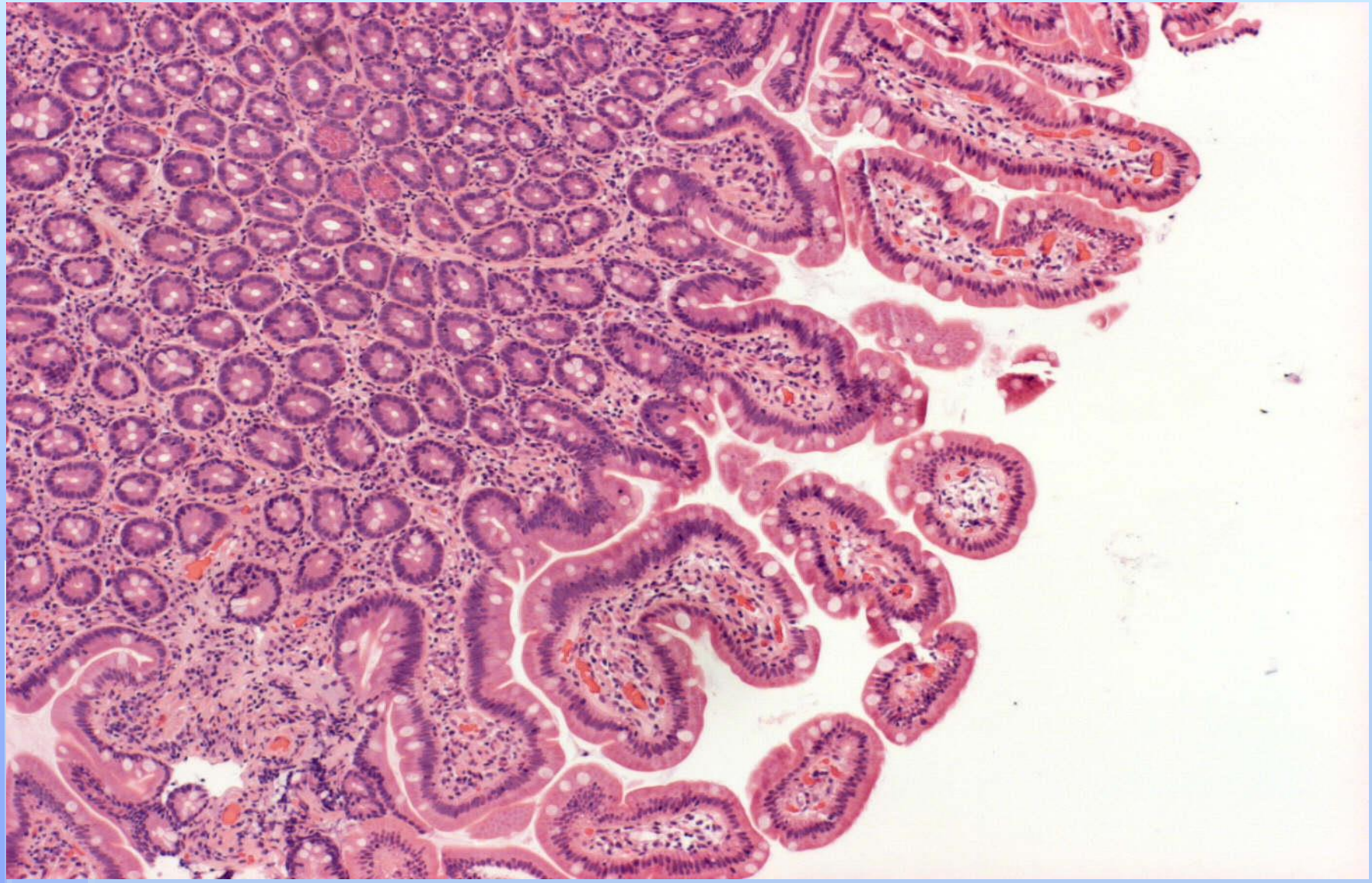
March 2003

- Developed pain in Rt ischial tuberosity
- Interfered with work and ability to sit for any time e.g. long car journeys
- Seen by Rheumatology : No pathology identified

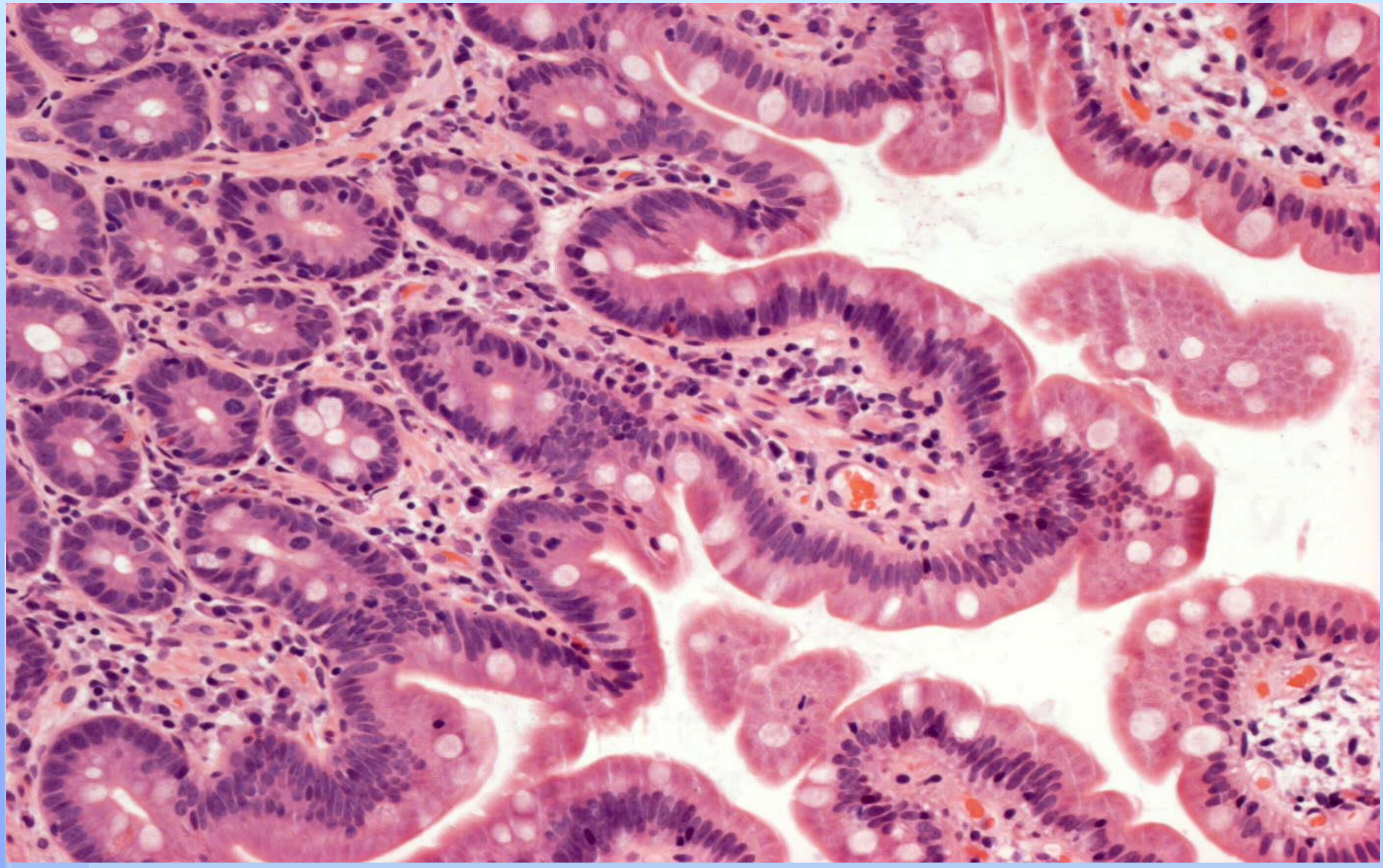
July 2003

- Had an episode of diarrhoea , no pathogen identified.
- Referred to Gastroenterology upper and lower GI endocsopy were normal.

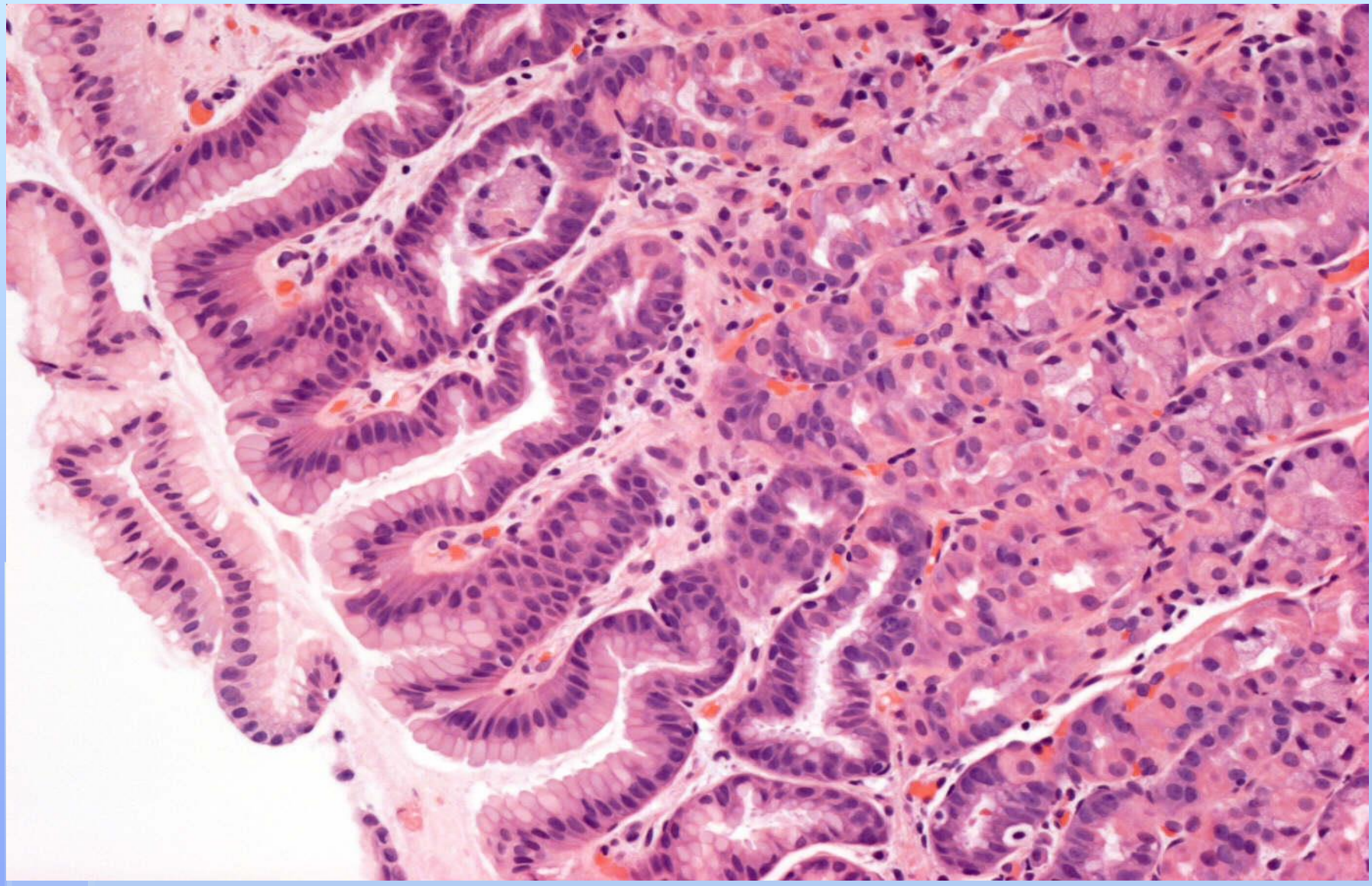
Duodenal biopsy 1



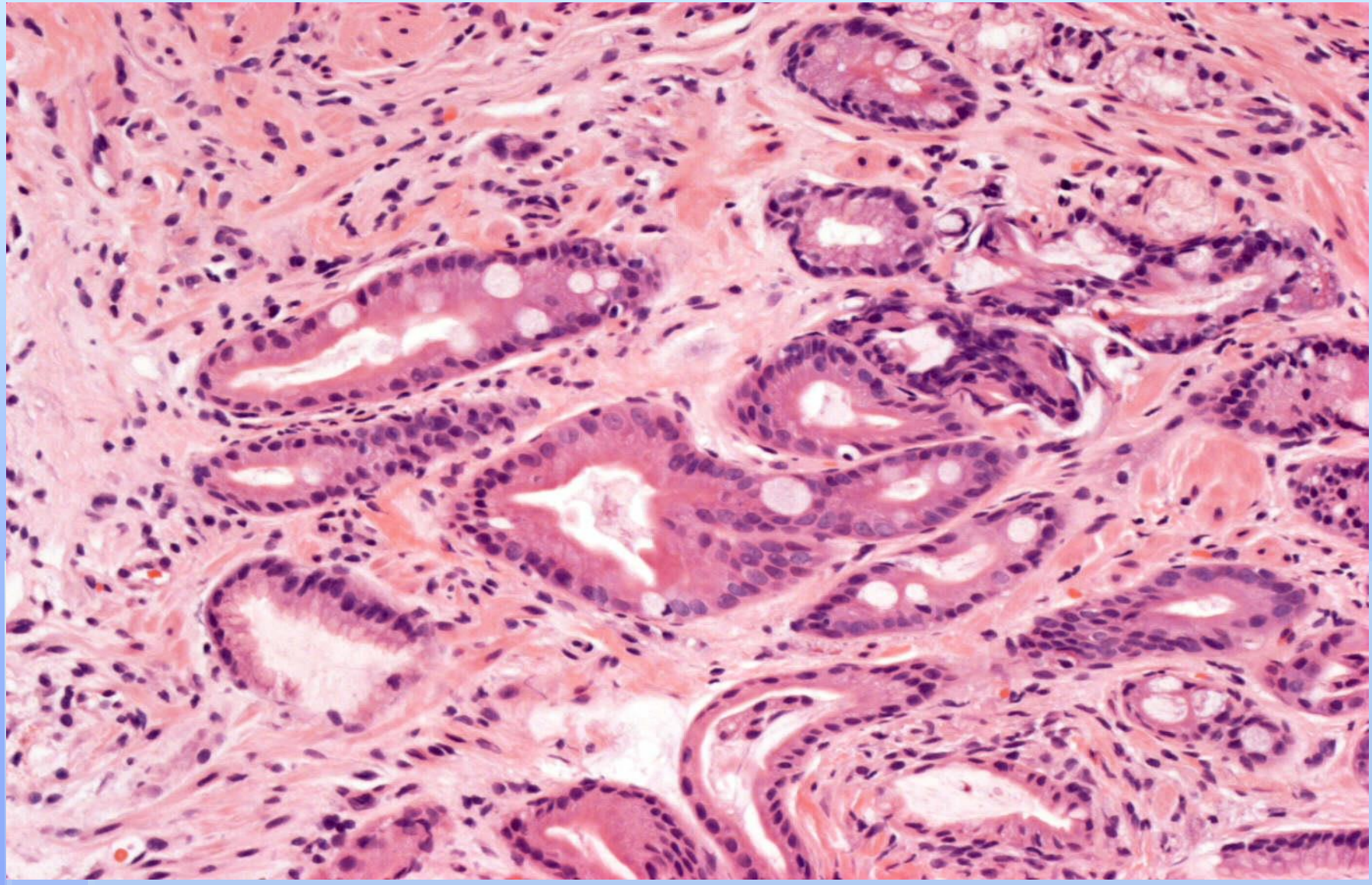
Duodenal biopsy 2



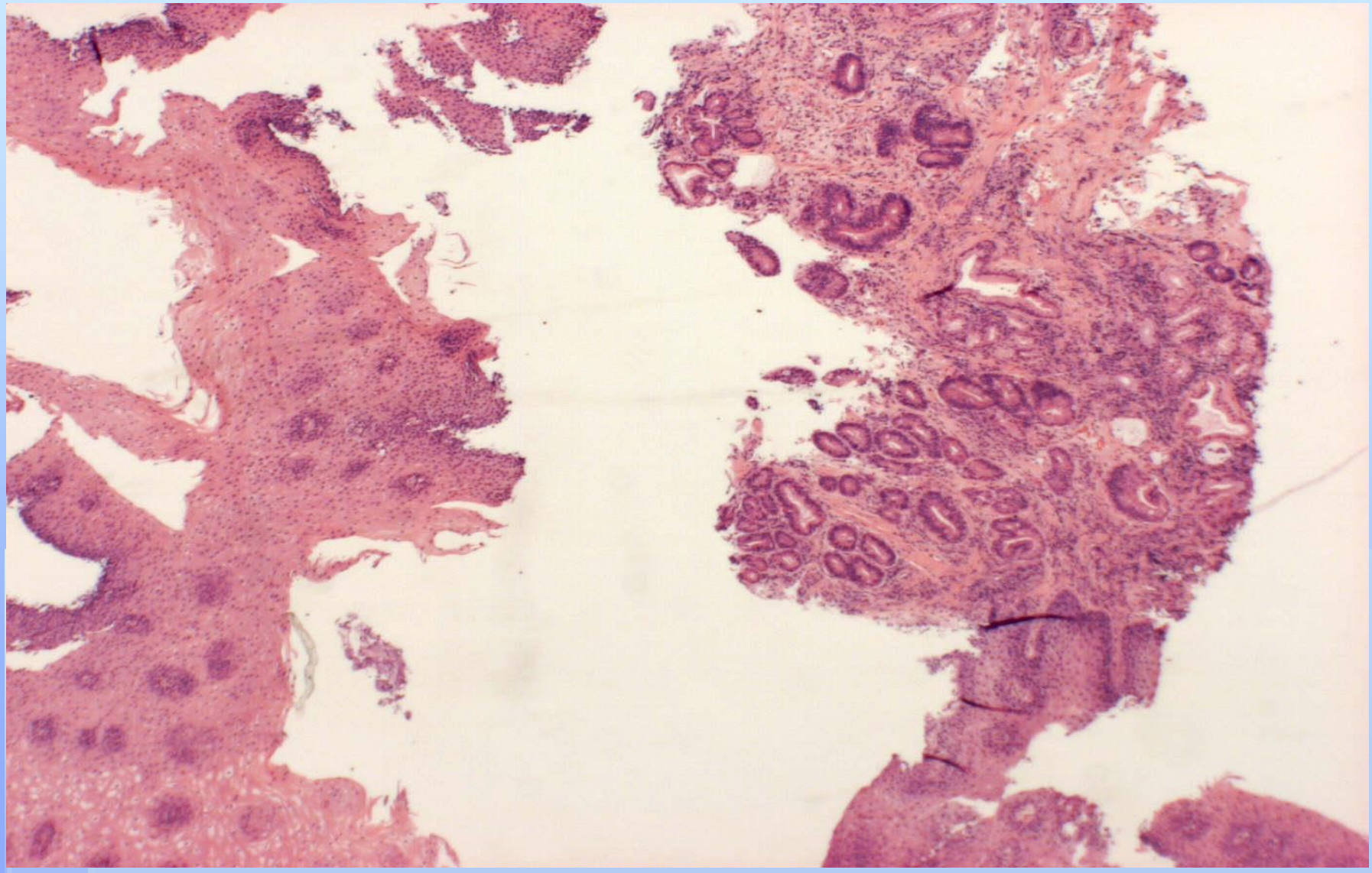
Stomach biopsy 1



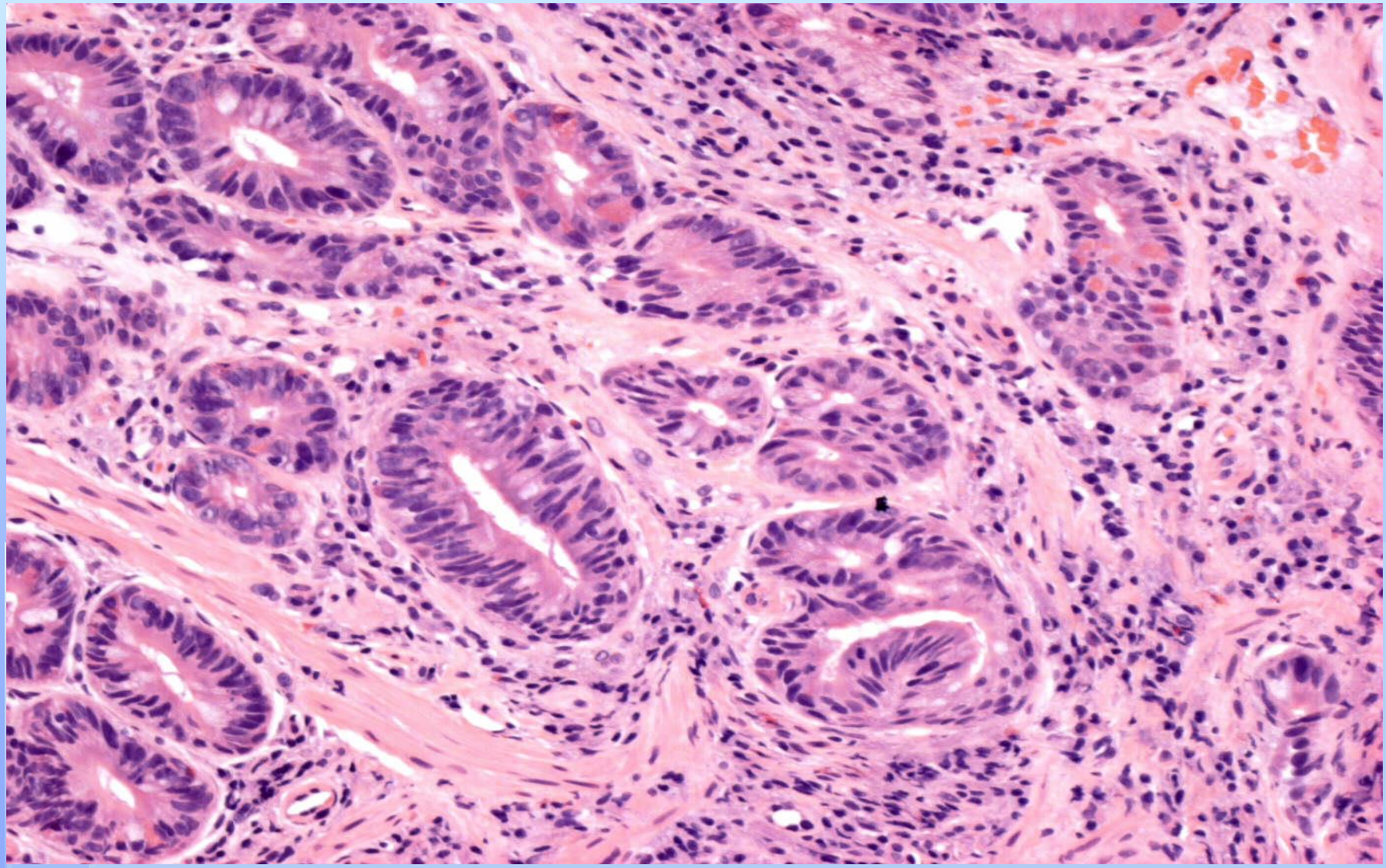
Stomach biopsy 3



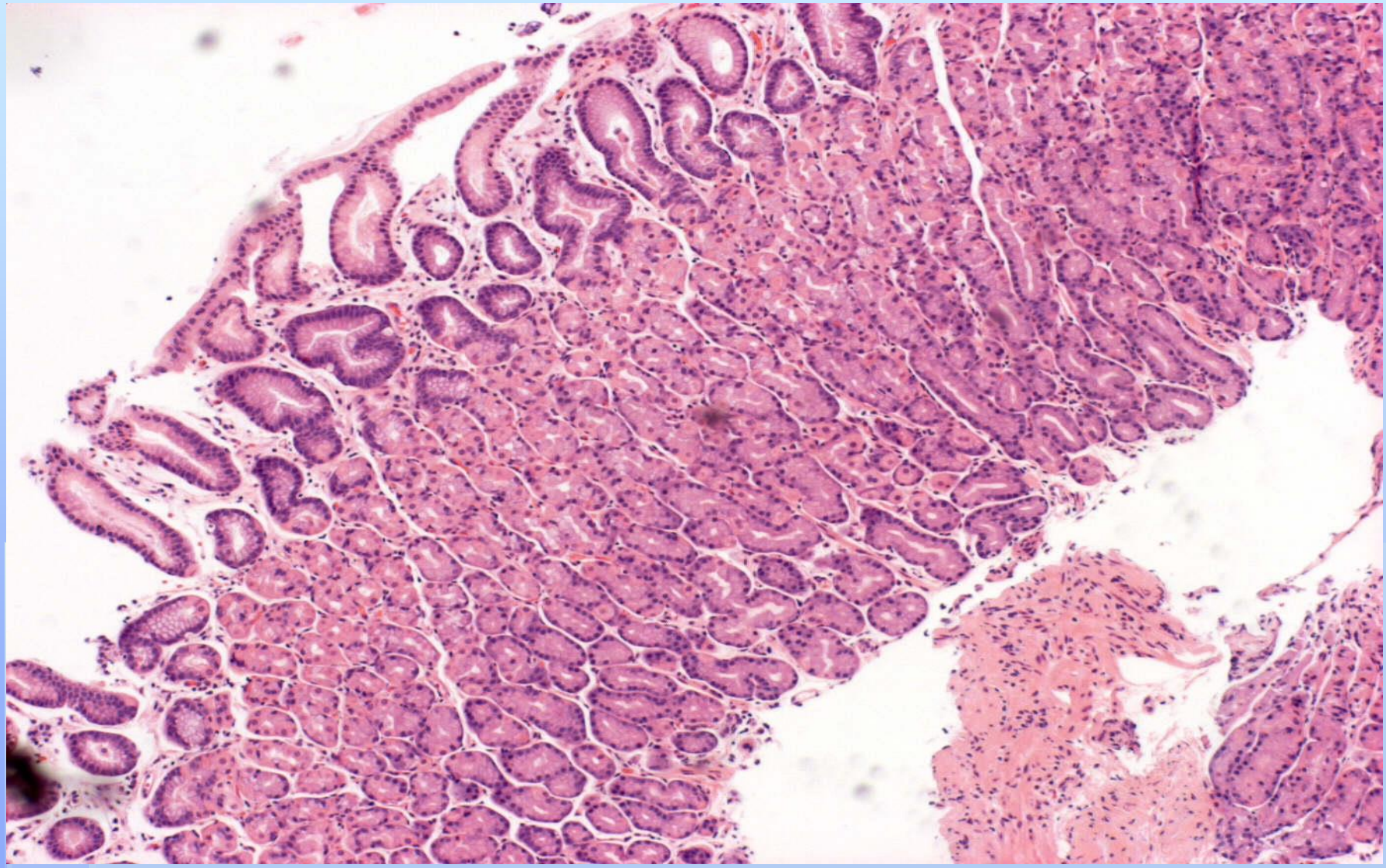
Oesophagus 1



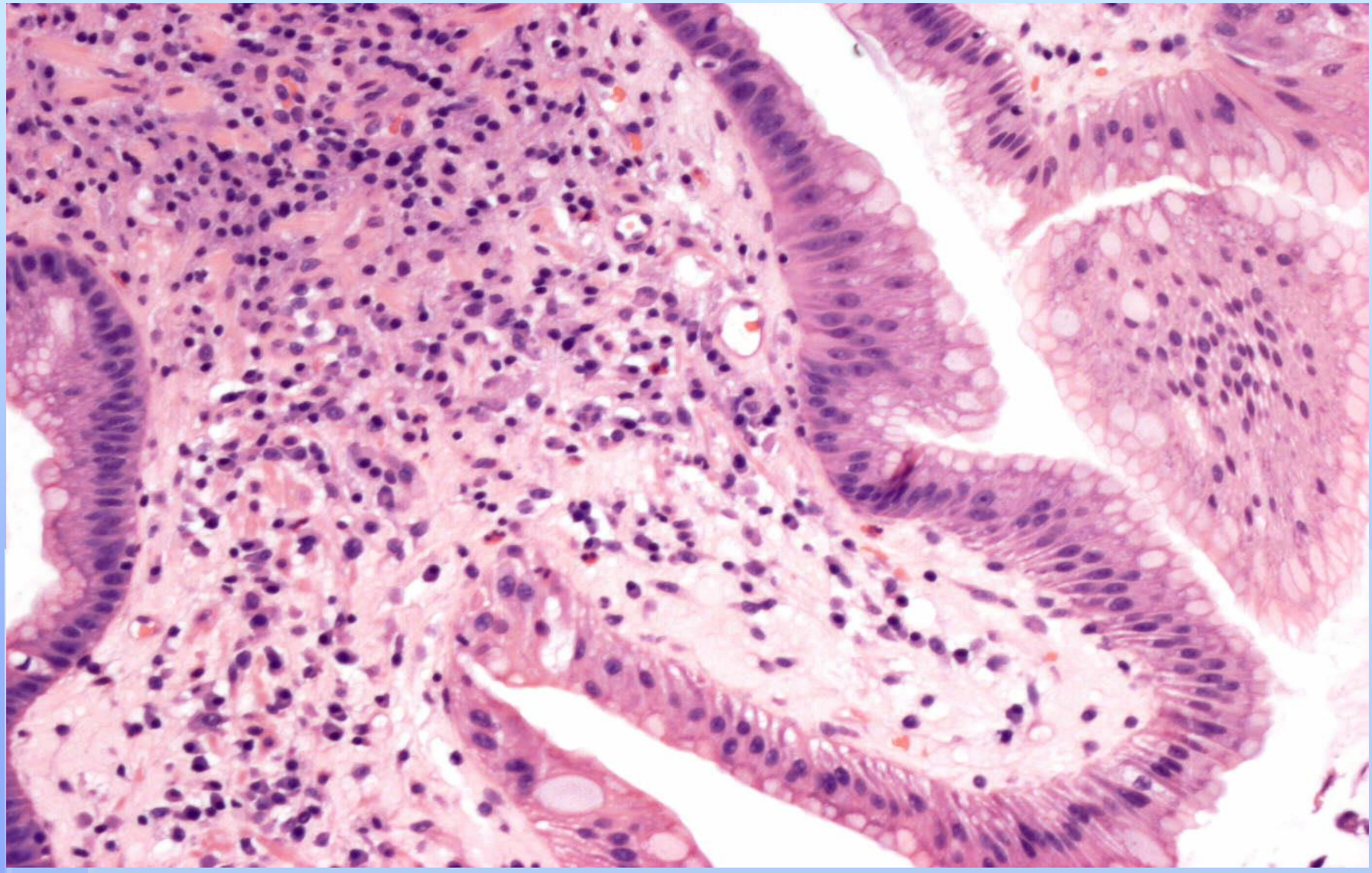
Oesophagus 2



Stomach biopsy 2



Oesophagus 3



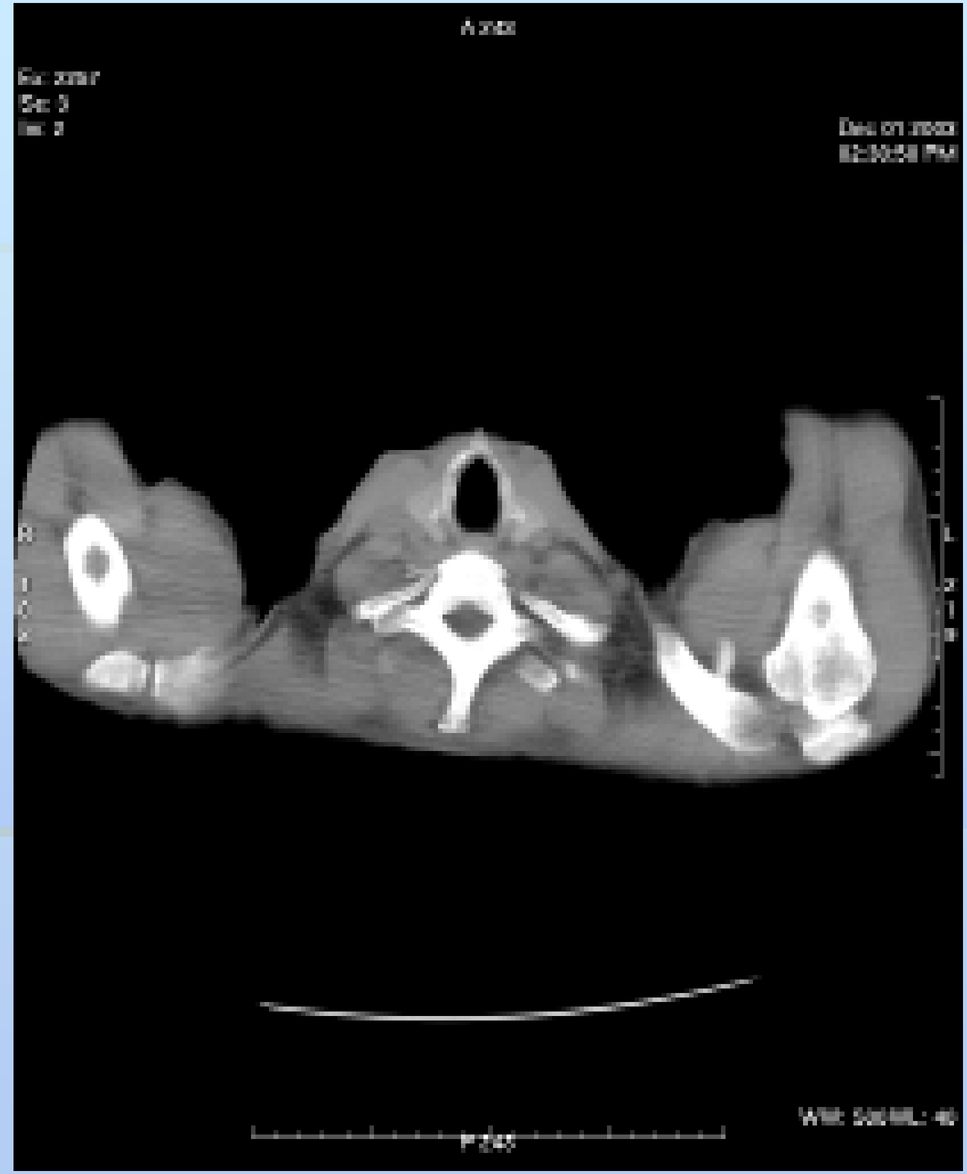
September 2003

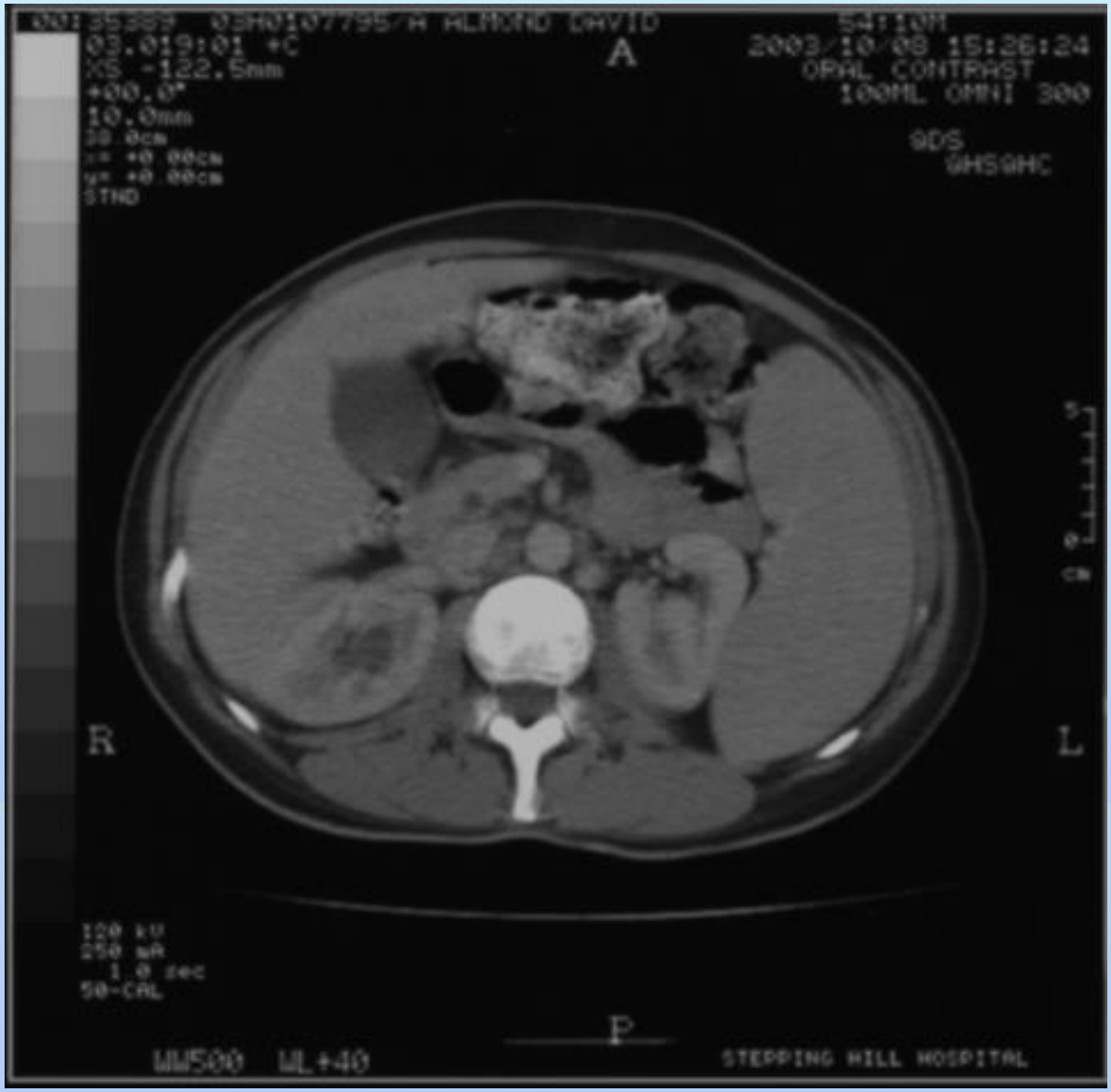
- Lump in Right Groin
- Worse over 2 weeks with hardening of right side of his scrotum which spread to the right inguinal area and Rt upper thigh..
- Hospitalised as clinically ? rapidly growing retroperitoneal mass

- **U/S**
  - Fluid between femoral shaft and tissue layers almost 1cm in depth
  - Marked oedema in pelvis and groin (esp. L side) diffuse throughout the tissue layers
  - Both testes normal with no evidence of hydronephrosis
  - Splenomegaly at 17cm .
  - No lymphadenopathy or ascites

- **CT**
  - Displaced left kidney
  - Minimal lymphadenopathy and no free fluid
  - Gallstones
  - ? Calcified mesenteric lymph nodes
  - Marked swelling of right obturator internus
  - Extending down thigh to insertion of abductors
  - Diffuse oedema within muscles

- Minor oedema in scrotum. Oedema involving left quadriceps in particular
- Abnormal bony texture
  - Irregular sclerotic pattern
  - Commented as probable systemic abnormality
- Normal lung bases

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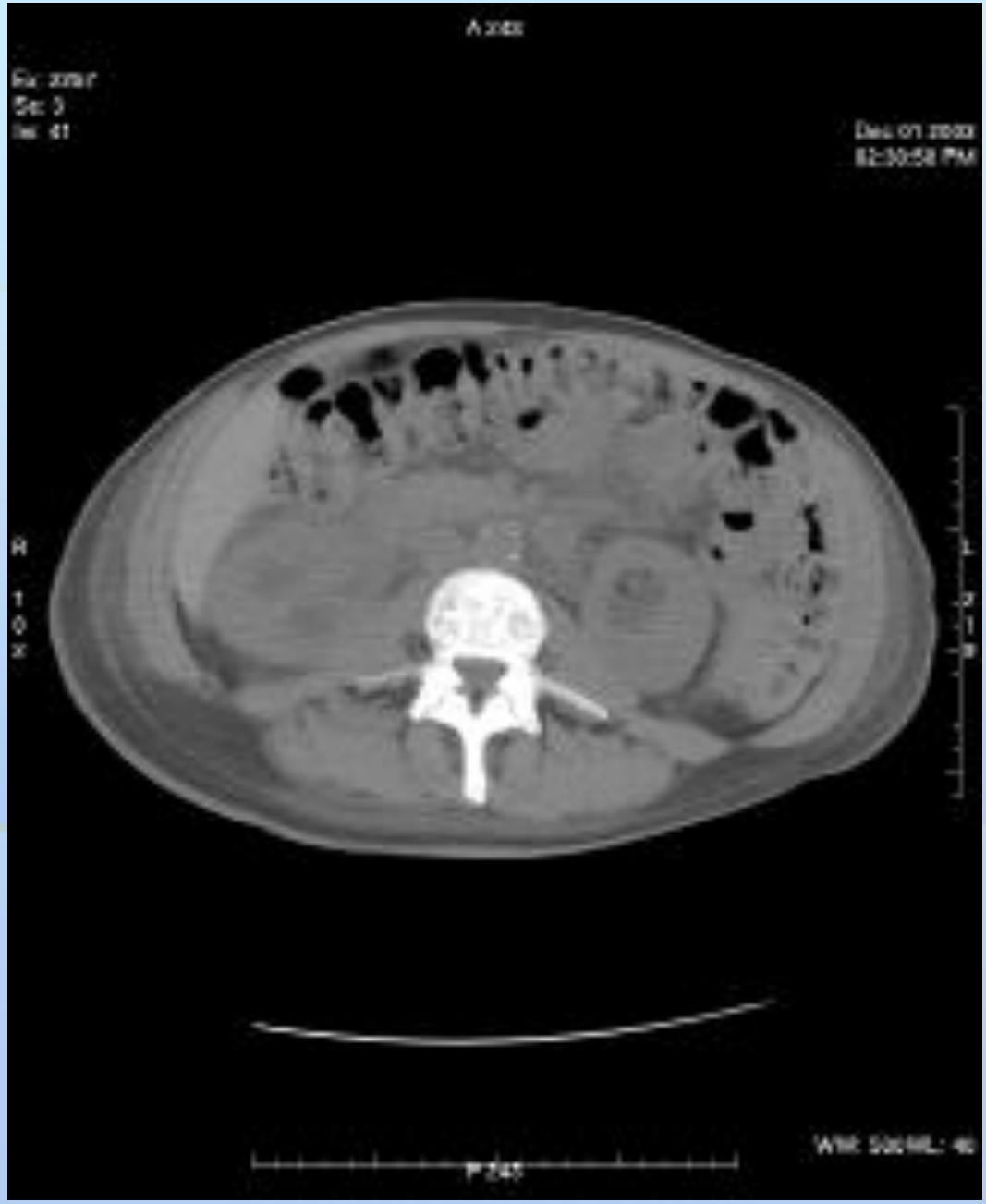
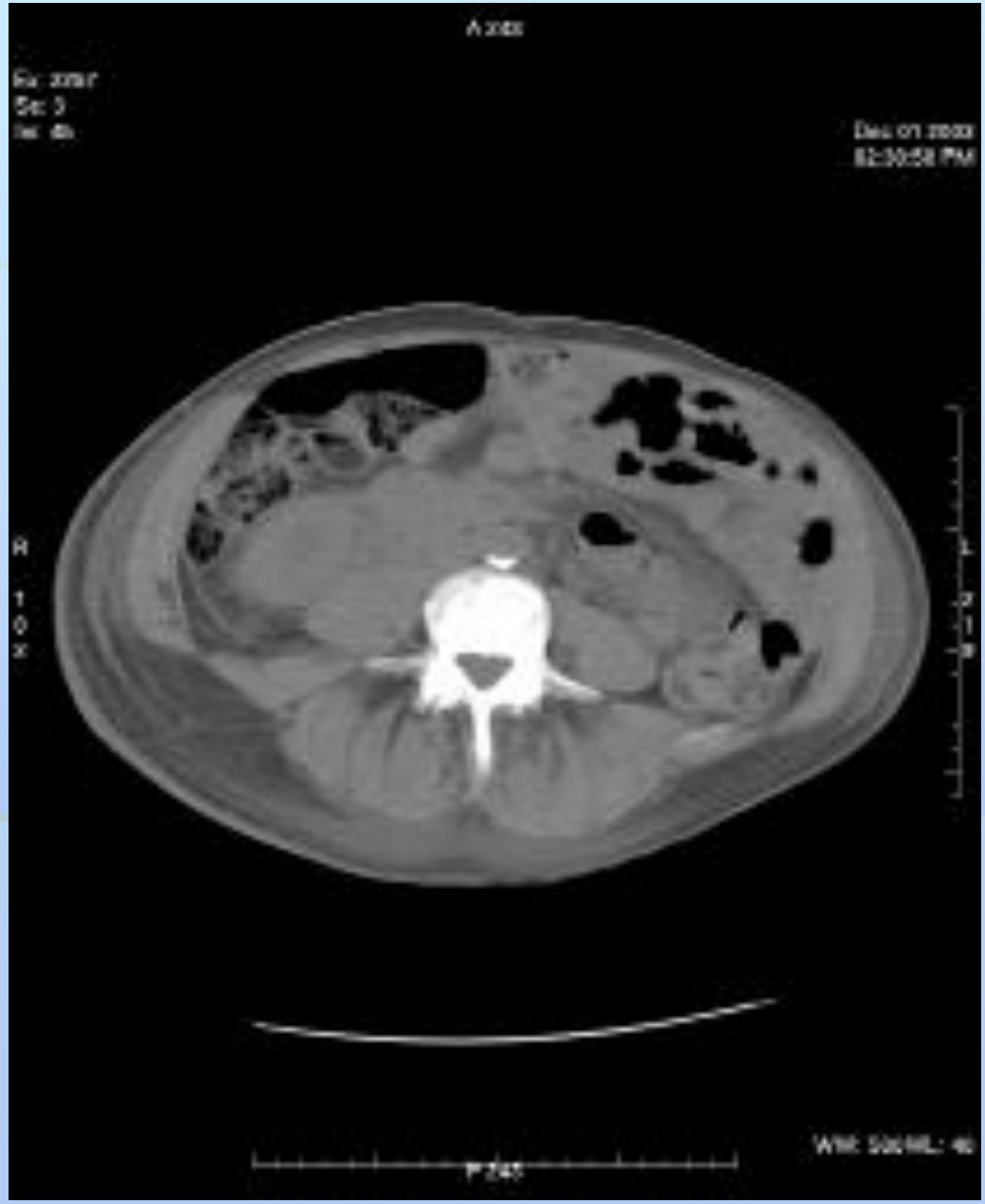
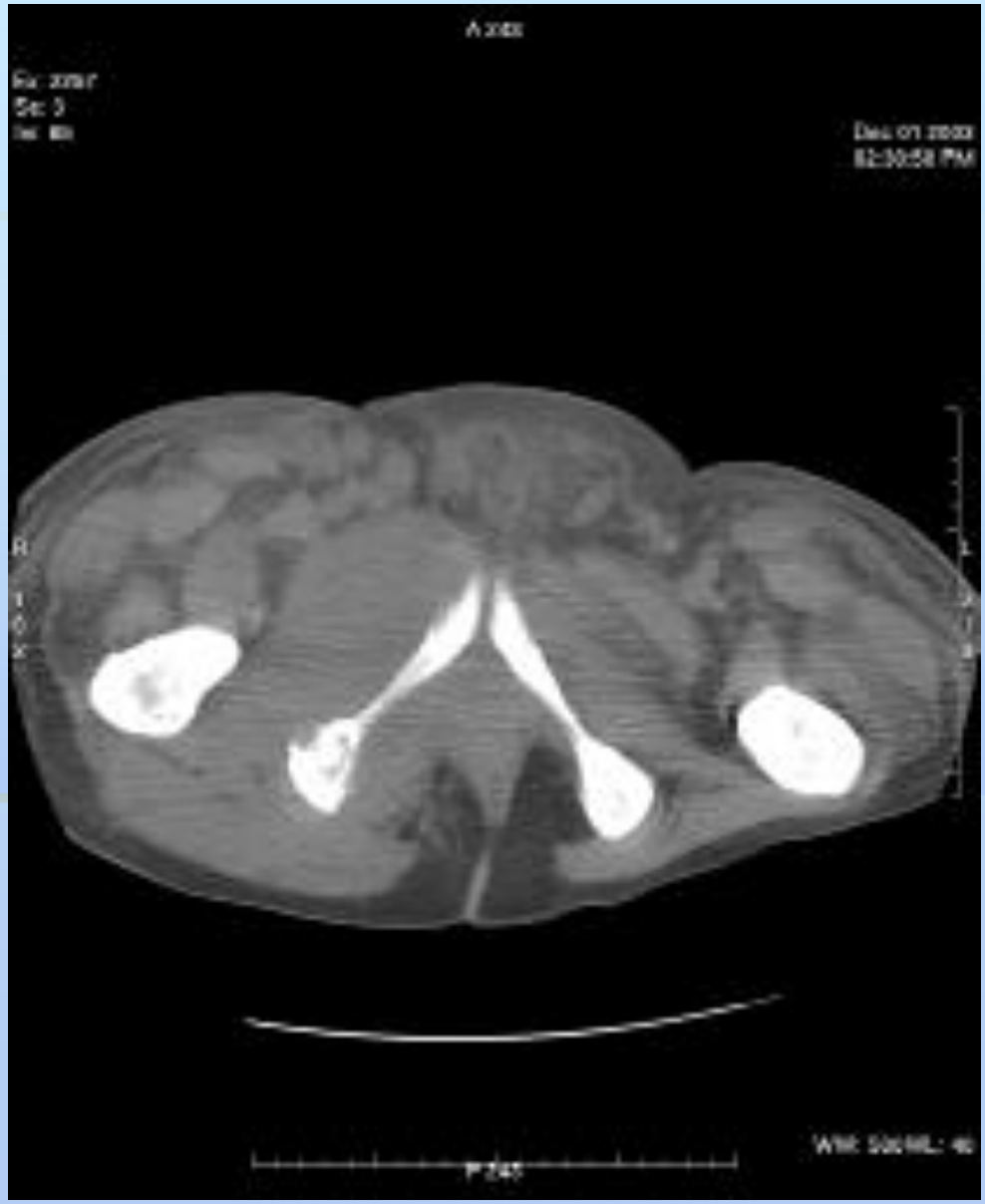
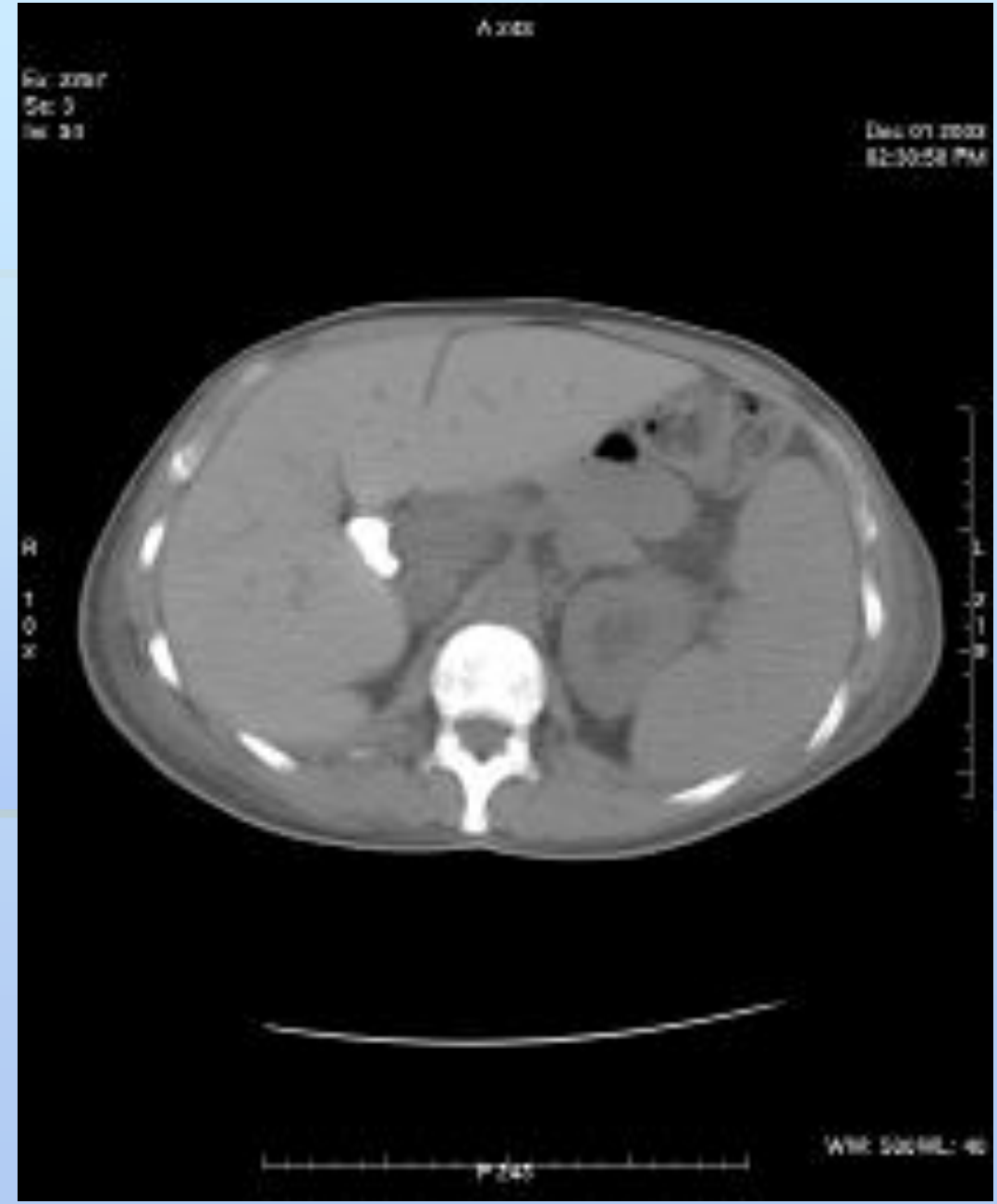
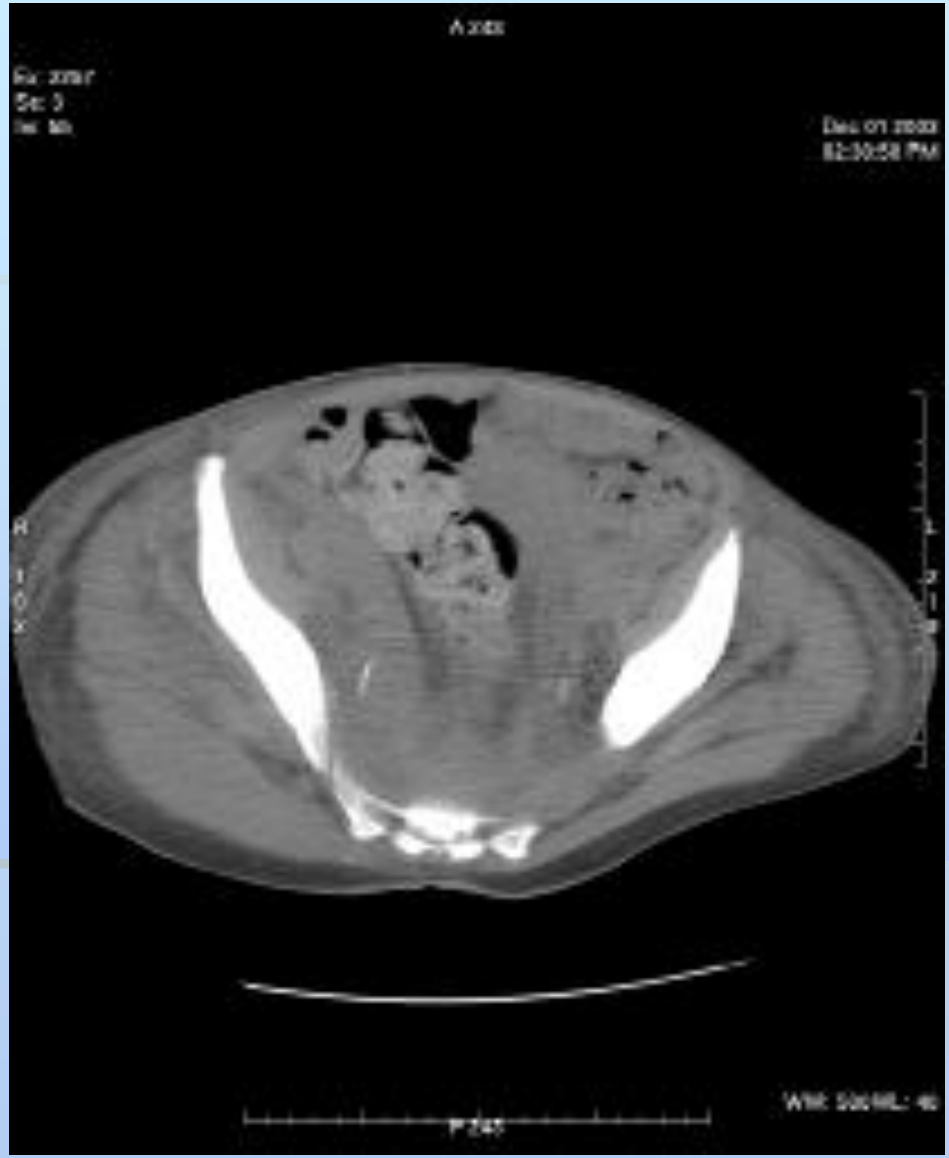
STEPPING HILL HOSPITAL

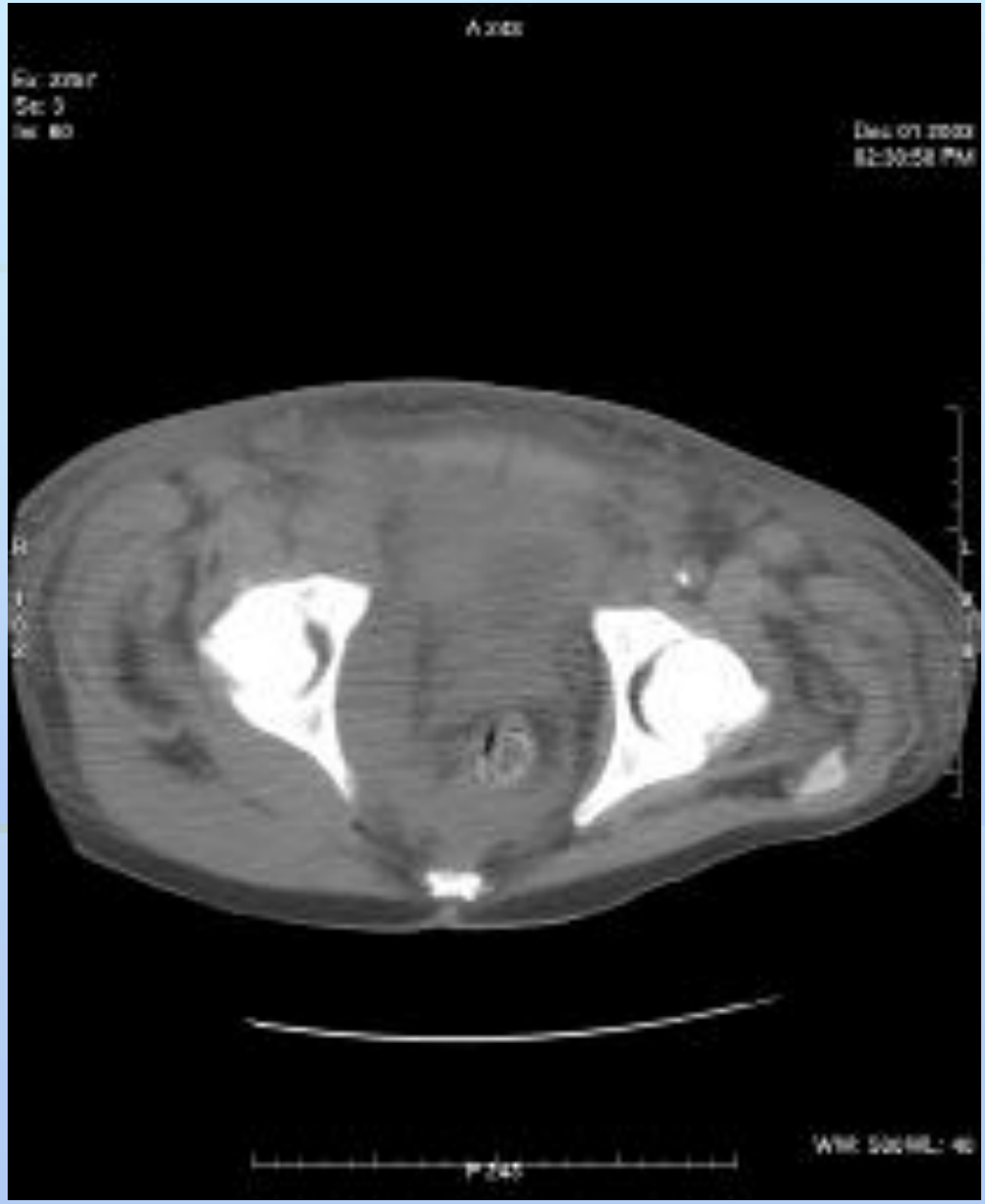


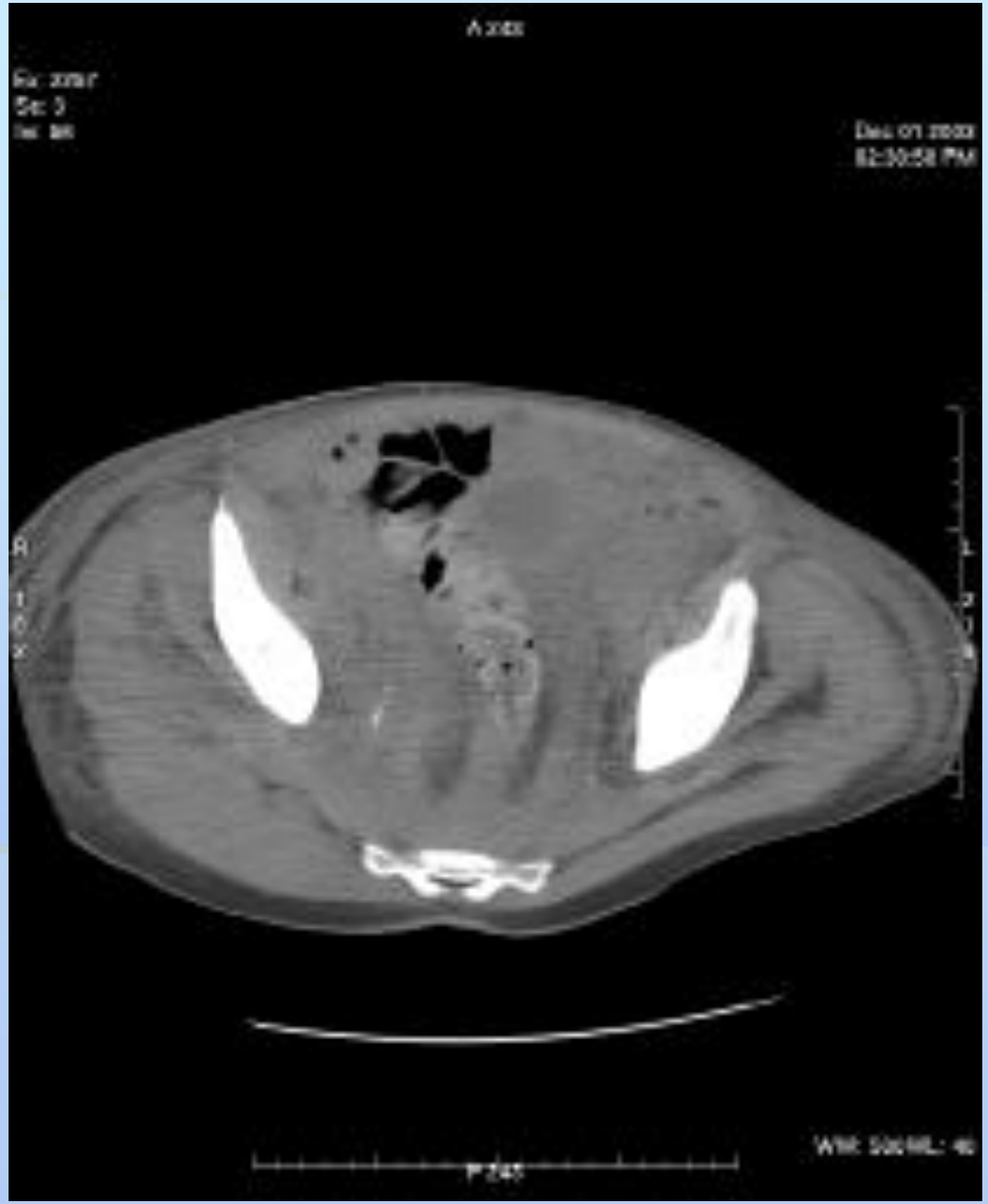


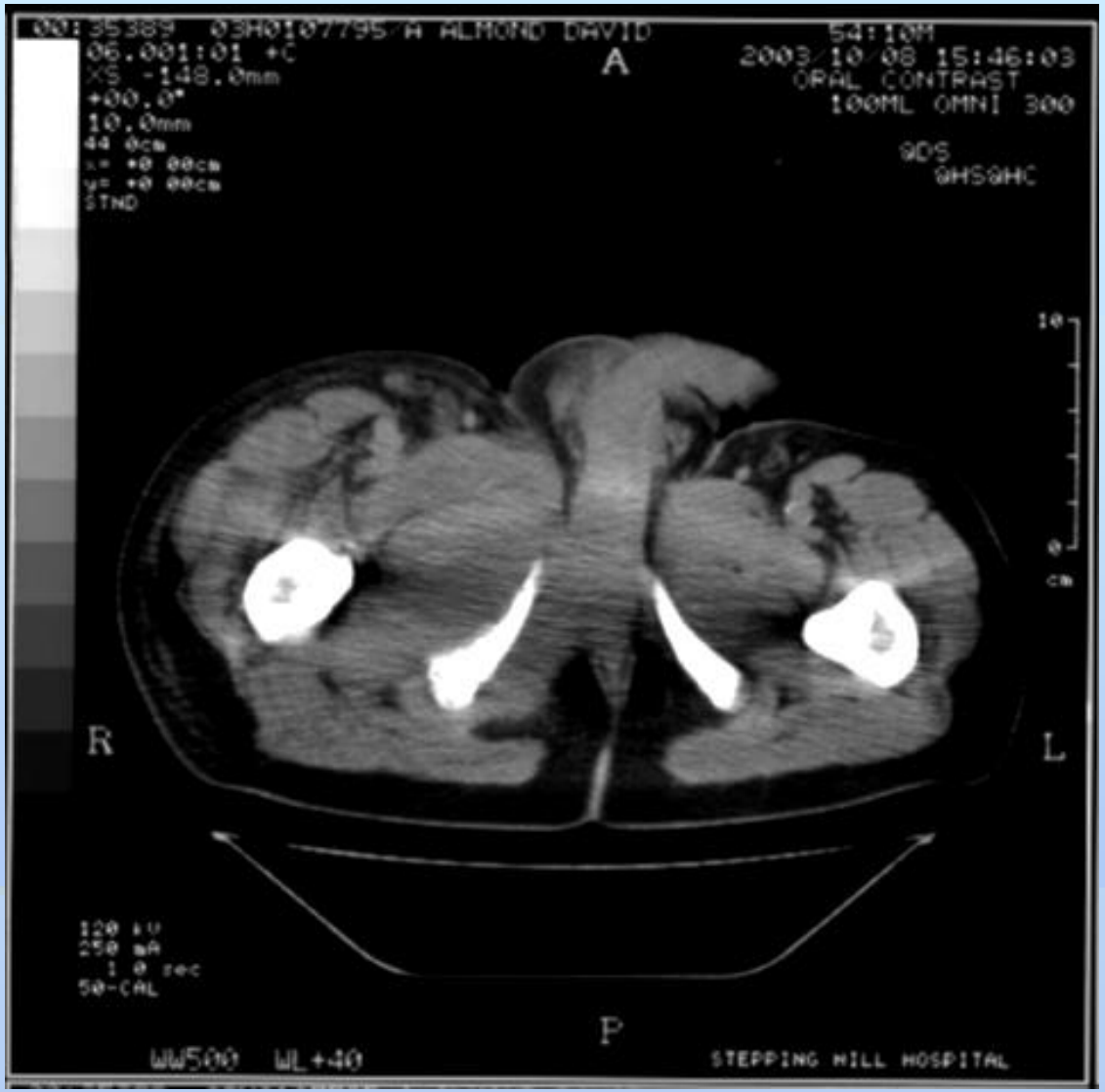








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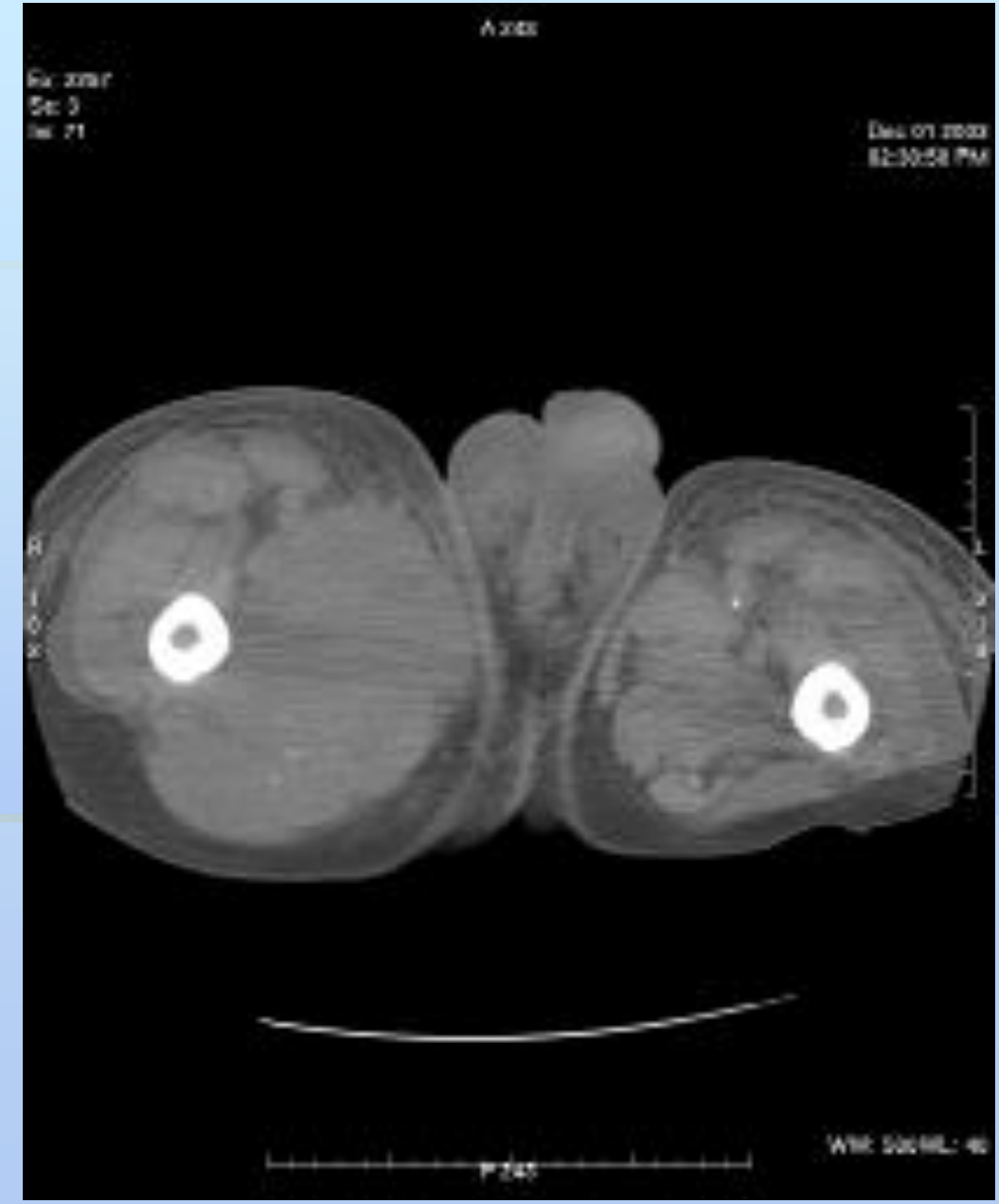
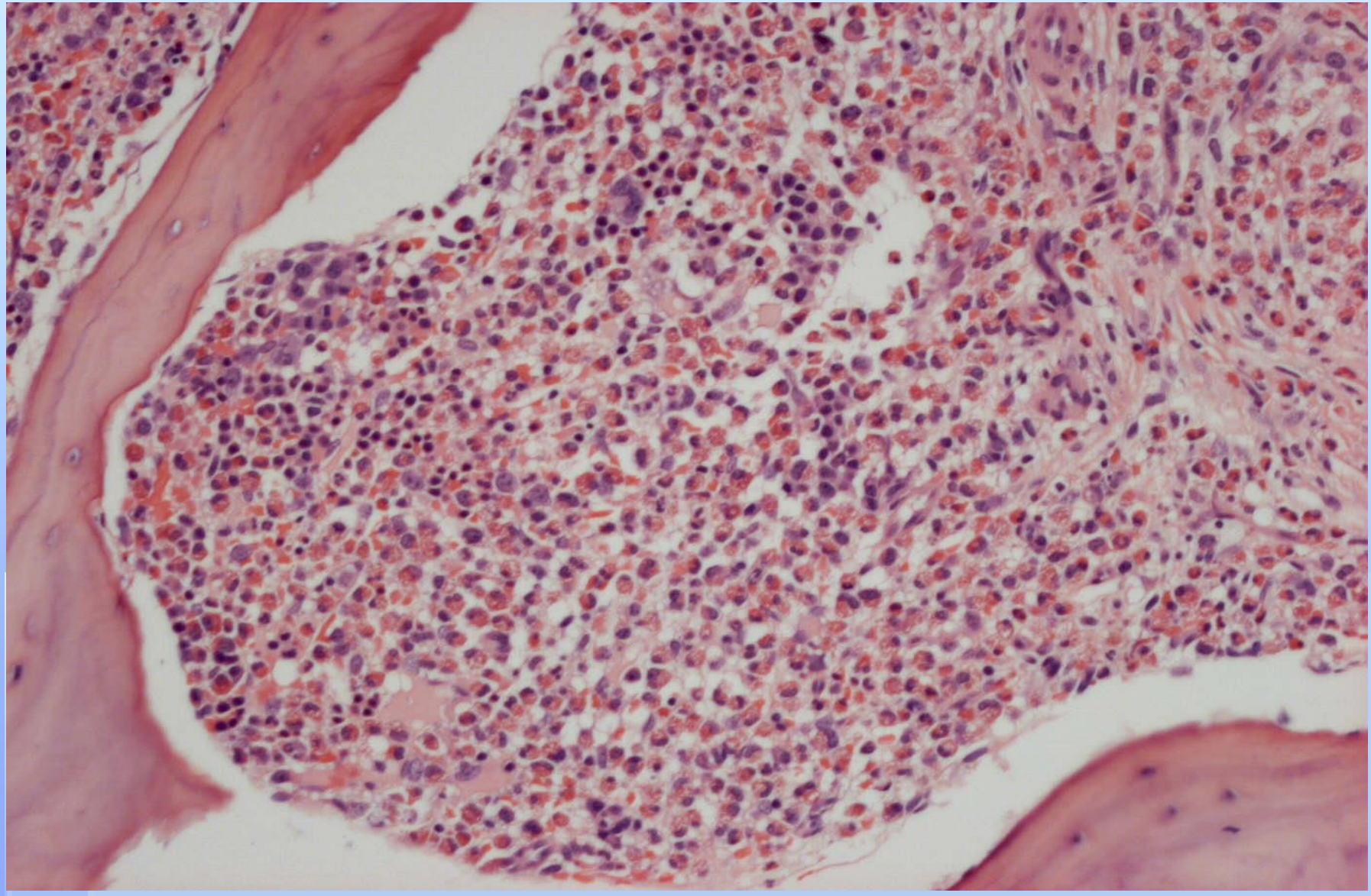


- **Clinical course**
  - Progression of oedema of right side from waist to toes
  - Diagnosed ? Lymphoedema
  - Pain needed strong opioid analgesia
  - Doppler scans were negative for DVT.
  - Echocardiography was normal.

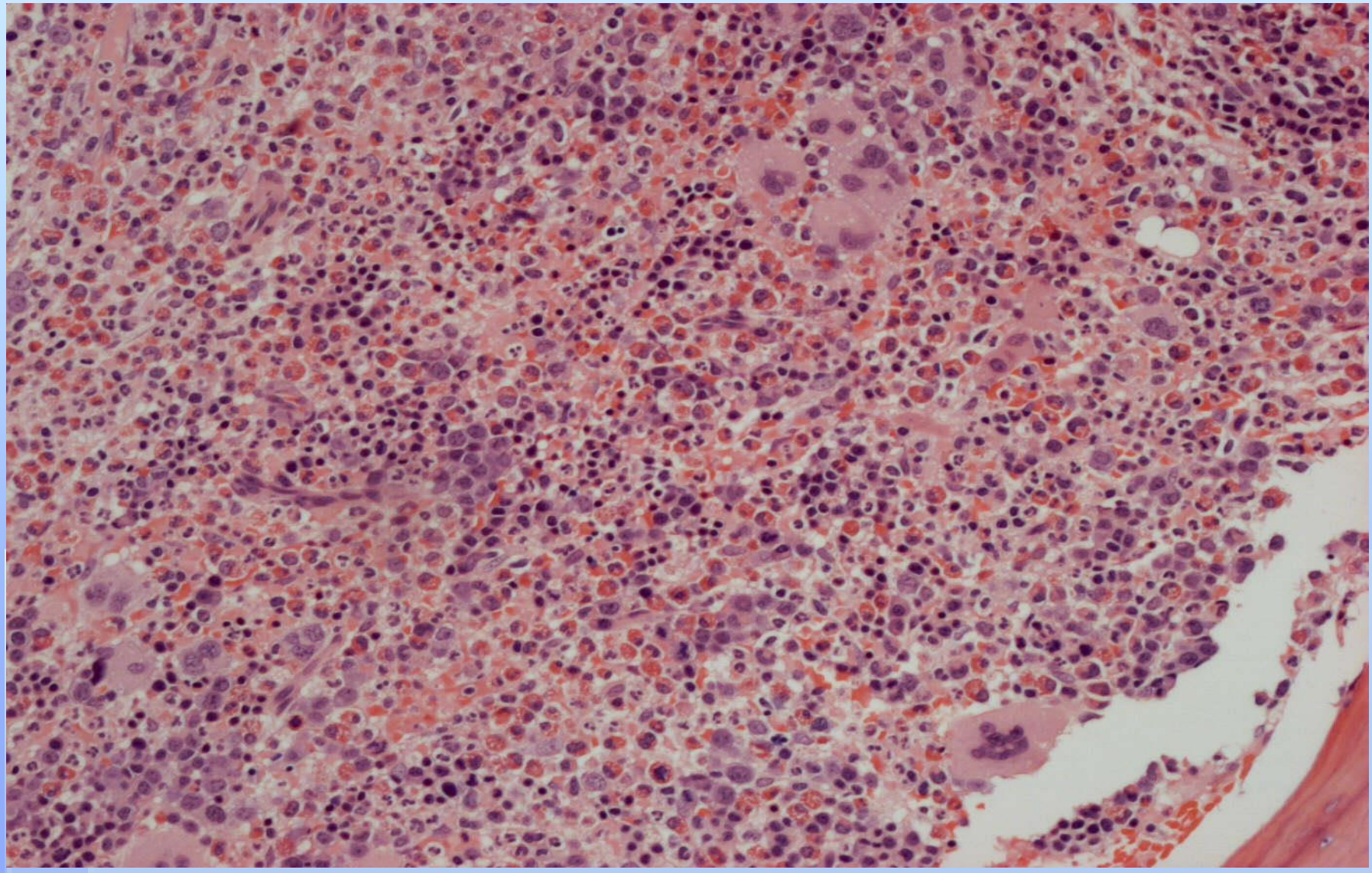
- Suffered pathological fracture to left femur while standing on one leg to pull on pyjamas.
- Leg pinned
- Bone marrow and fracture site biopsies confirmed
  - Hypercellularity
  - Increased eosinophilic precursors
  - Increased reticulin and fibrosis
  - Bone necrosis

- Continued to have subcutaneous swelling in other areas such as arms and legs
  - Left Biceps muscle biopsy done. Repeated search for parasites Neg.
- Dramatic weight loss of 3-4 stone
- No occult malignancy identified
- Normal Igs (Normal IgE)
- No lymphoid T or B cell clone on marrow cell markers.Normal cytogenetics.

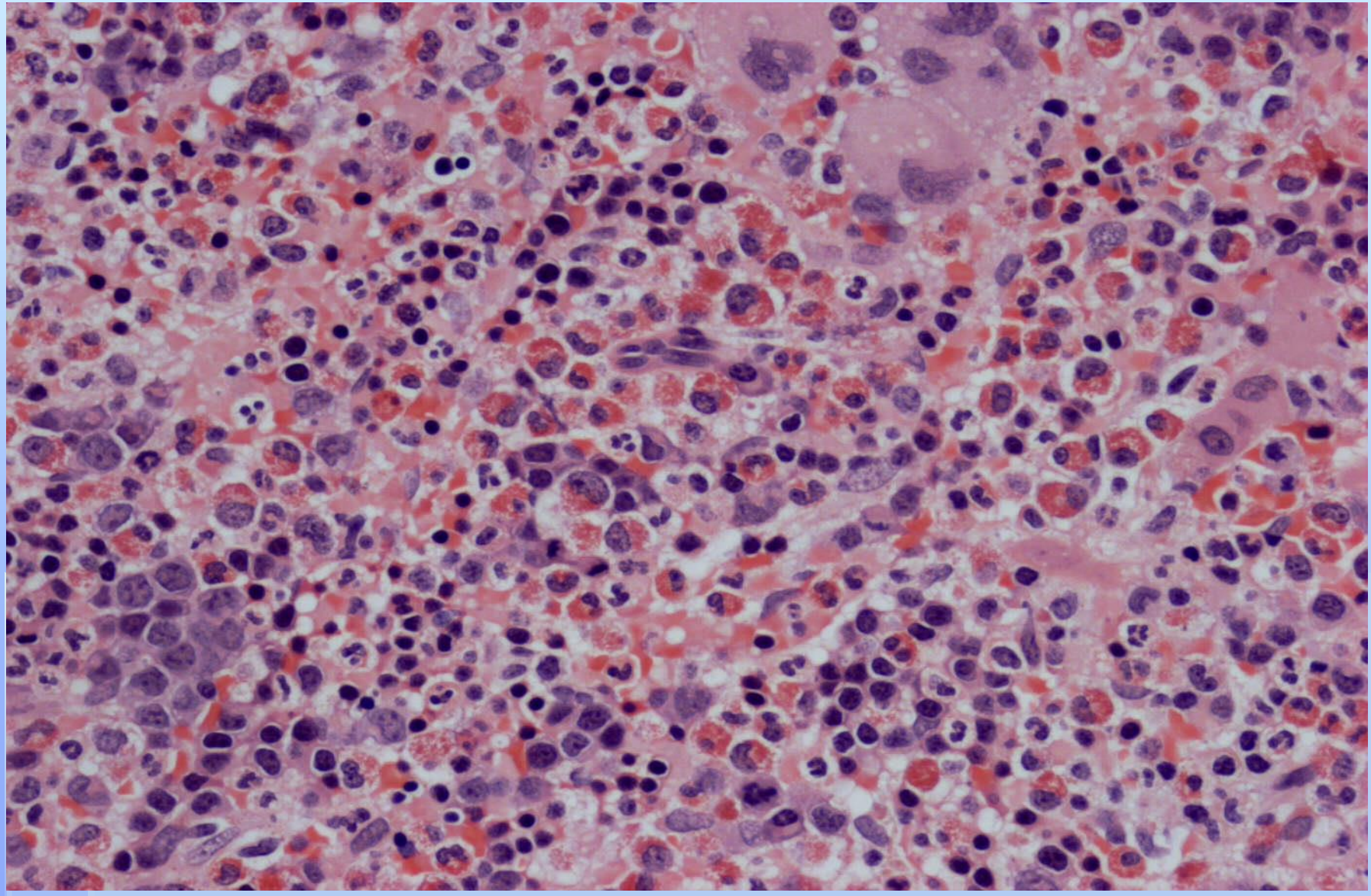
Trephine 1/1



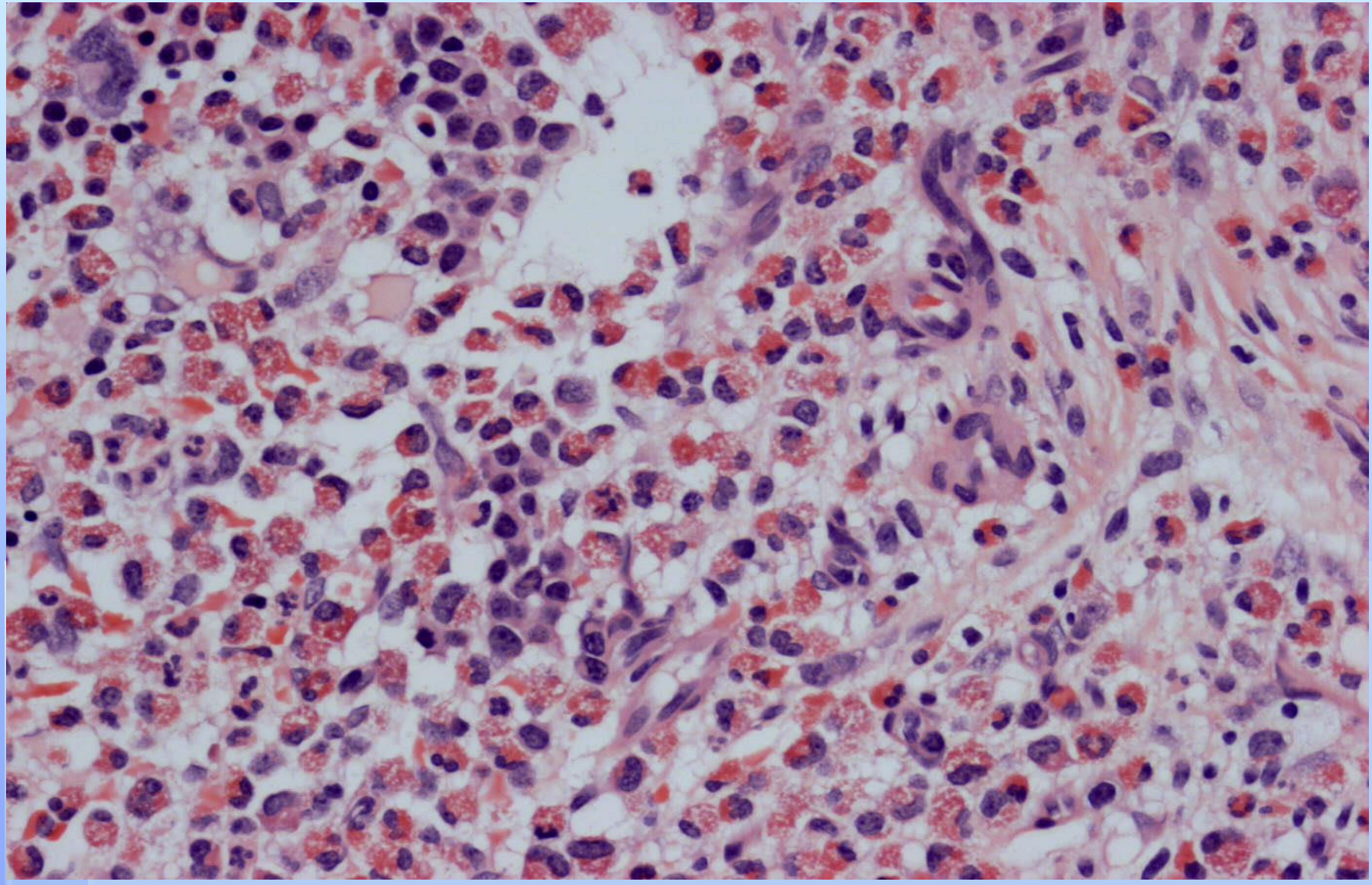
Trephine 1/3



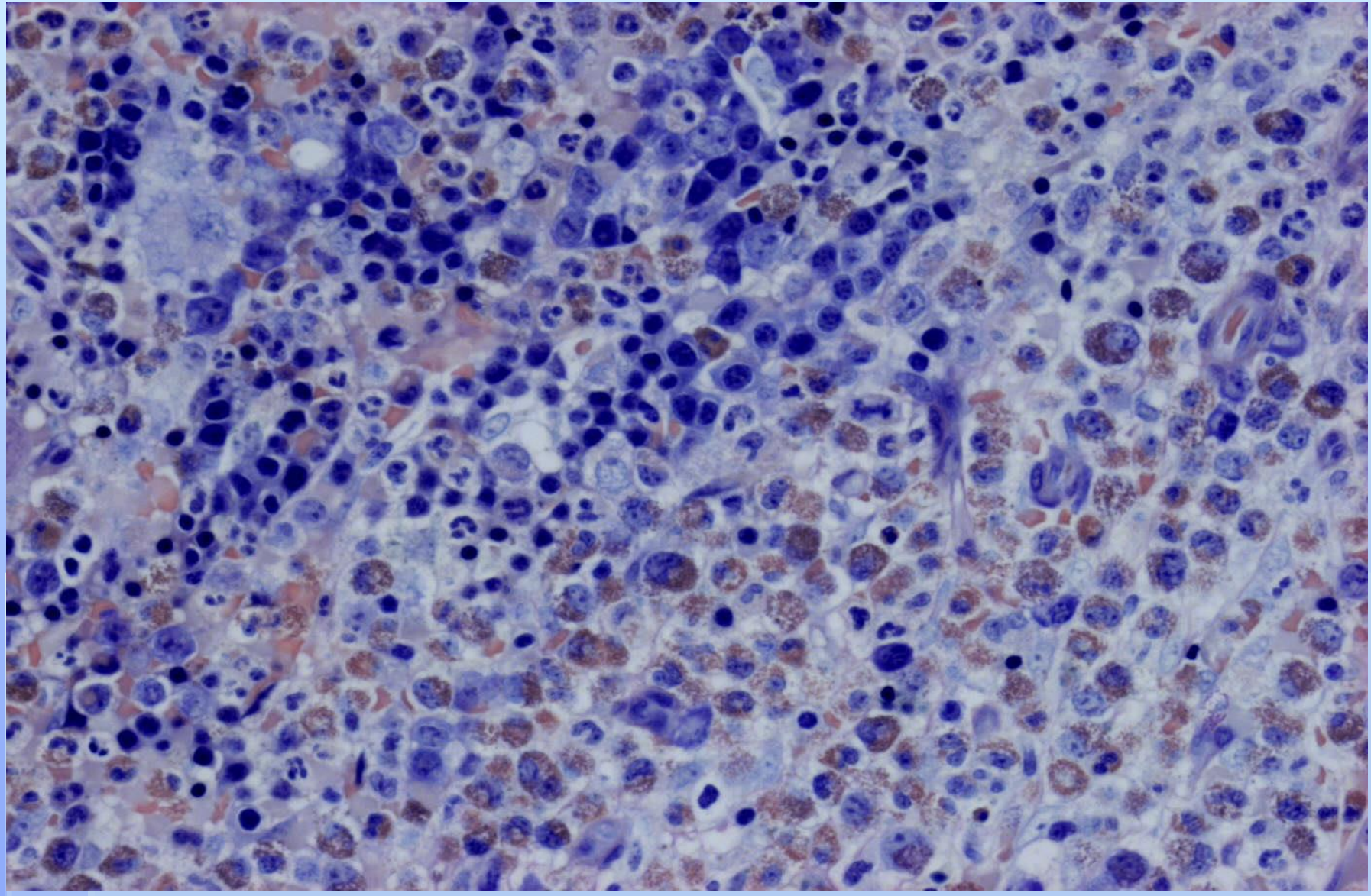
Trephine 1/4



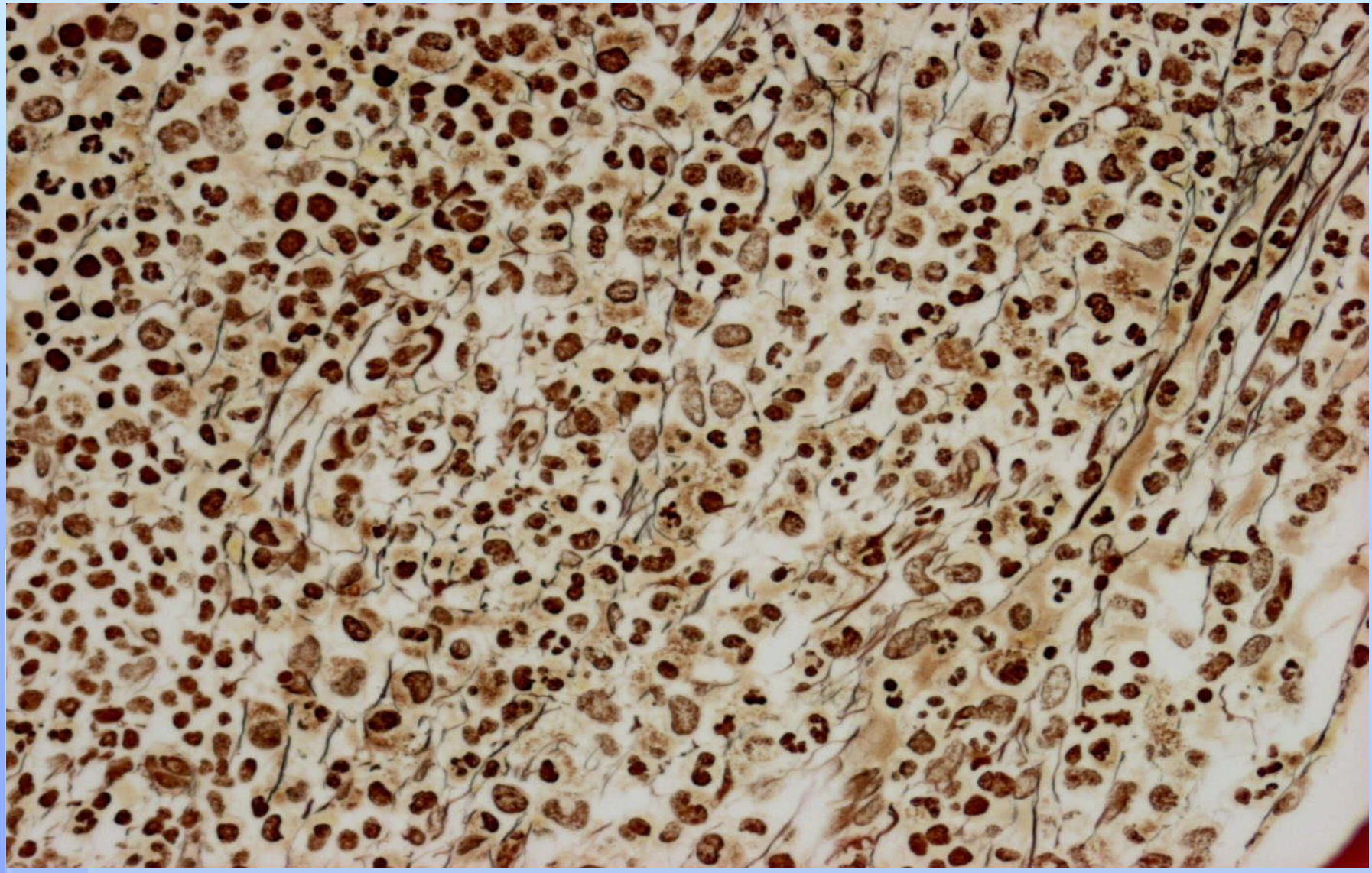
Trephine 1/5



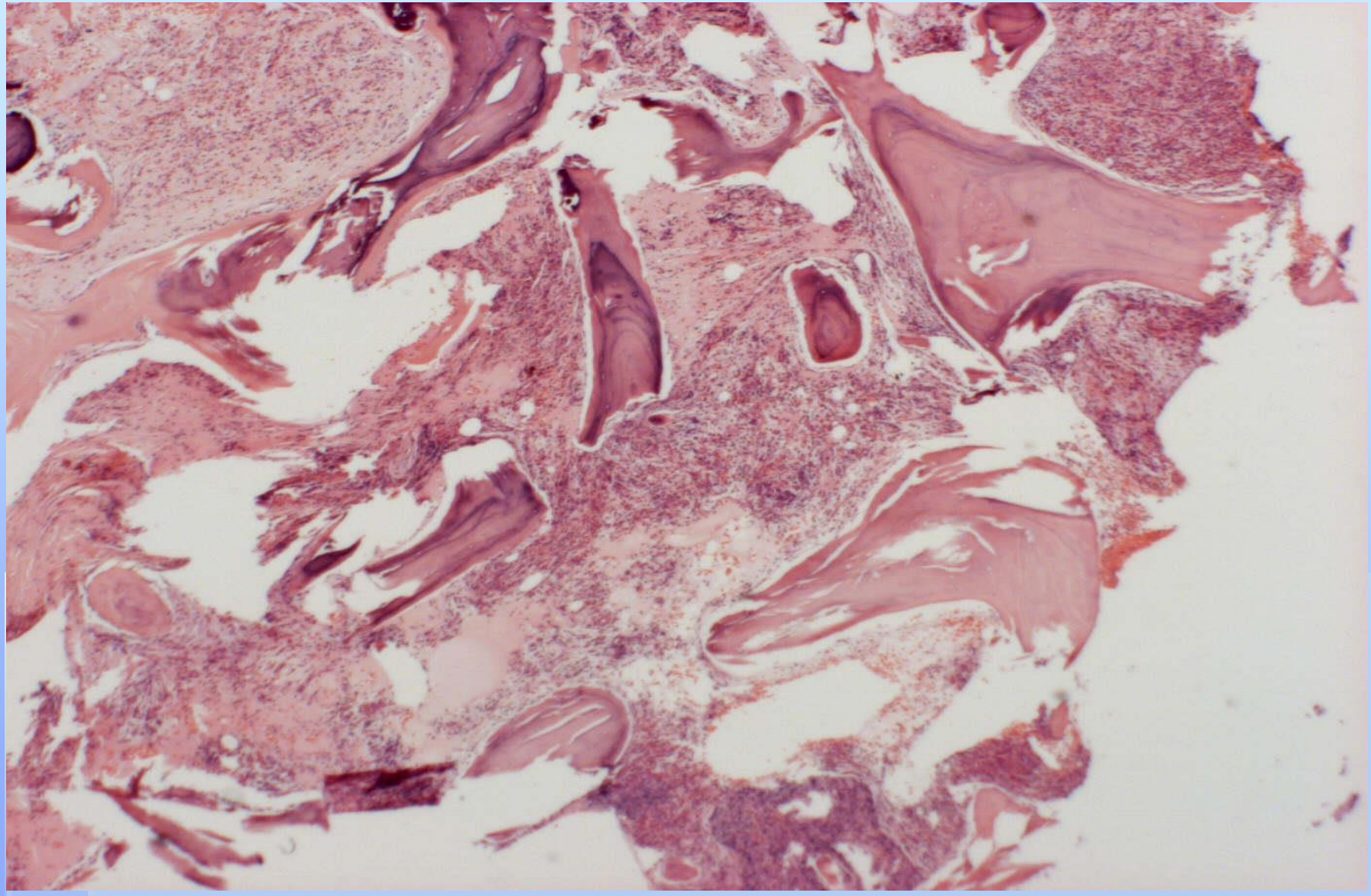
Trephine1 GIEMSA



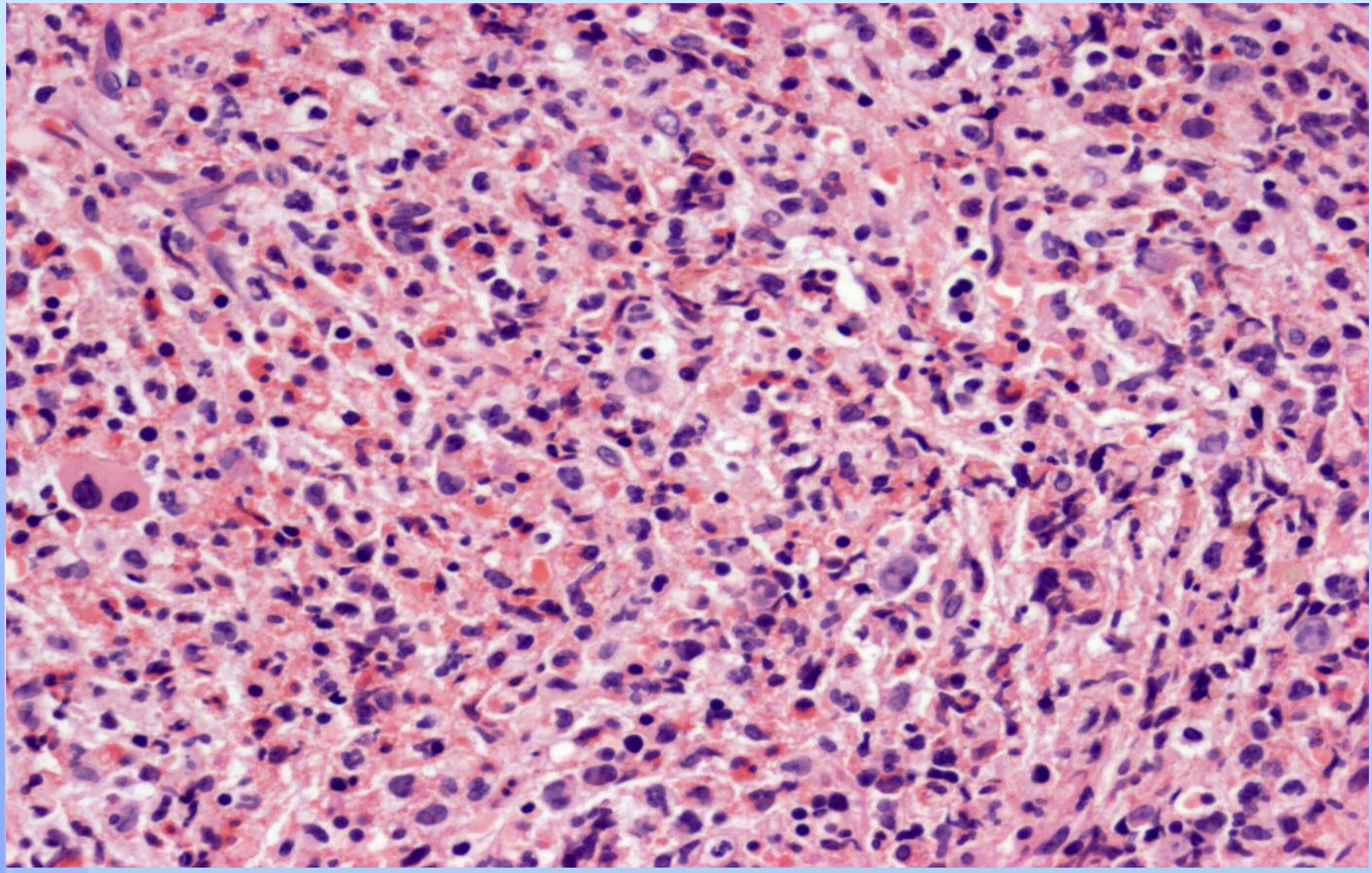
Trephine 1 RETIC



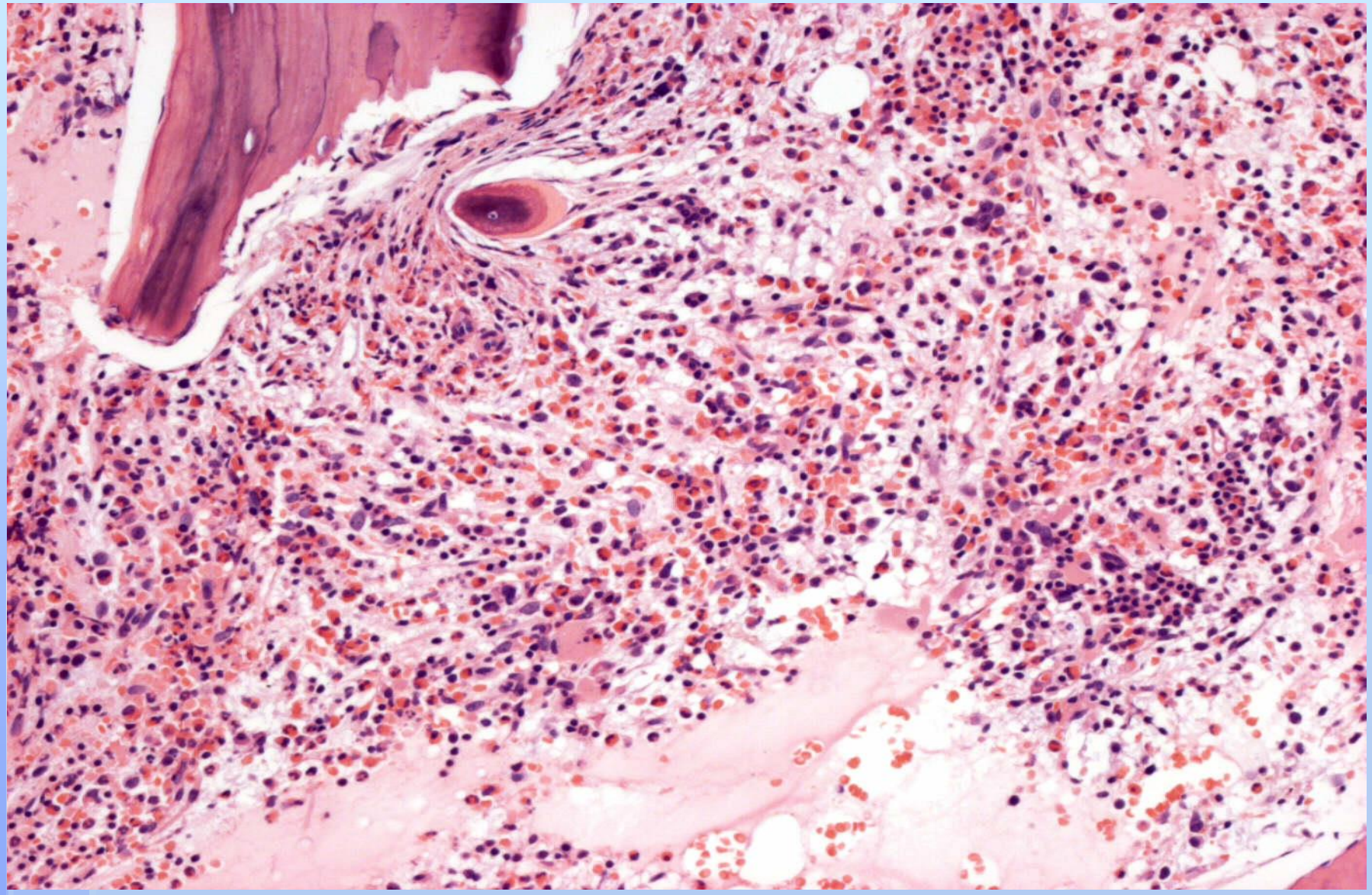
Fracture site 1



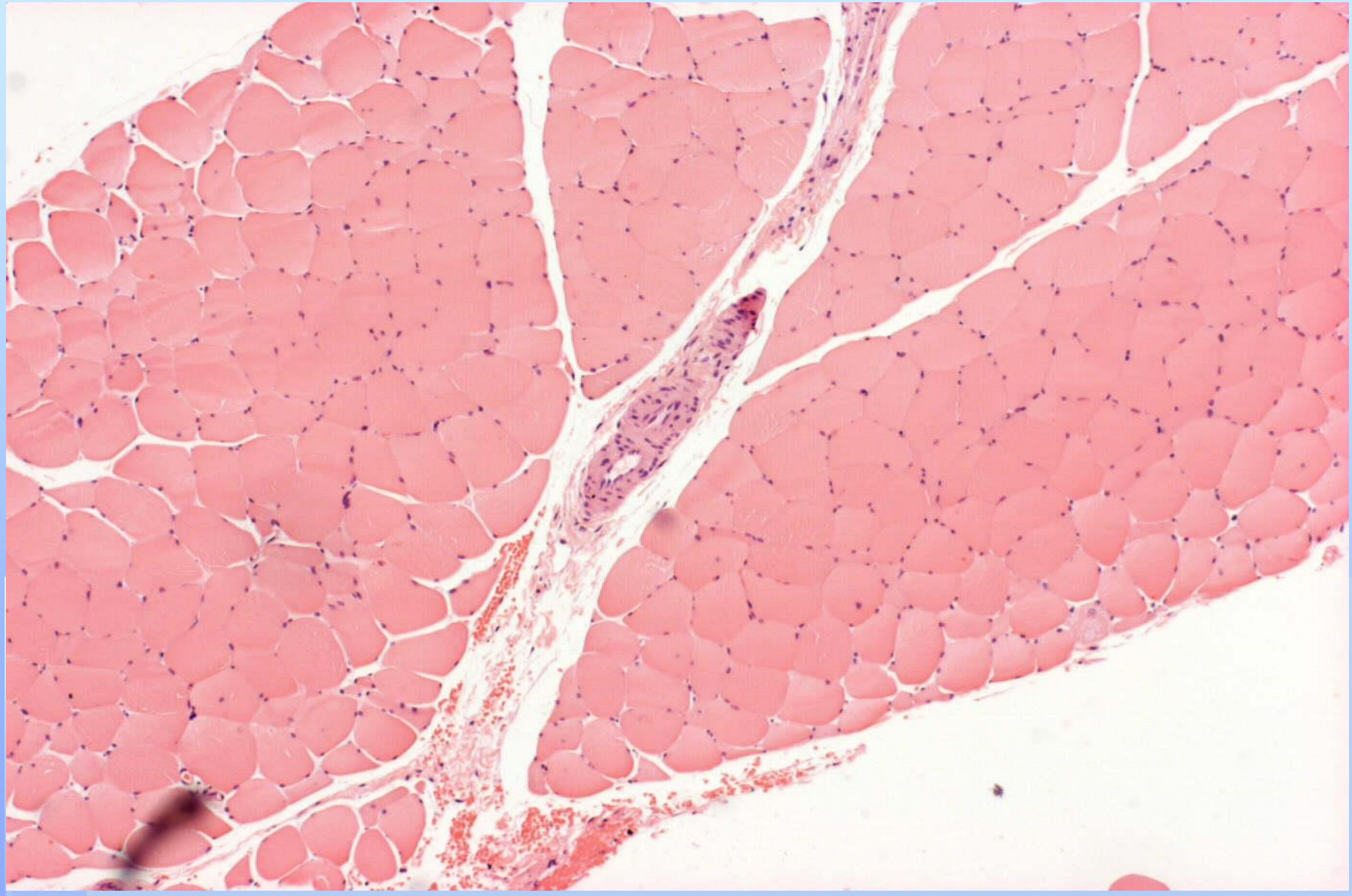
Fracture site 2



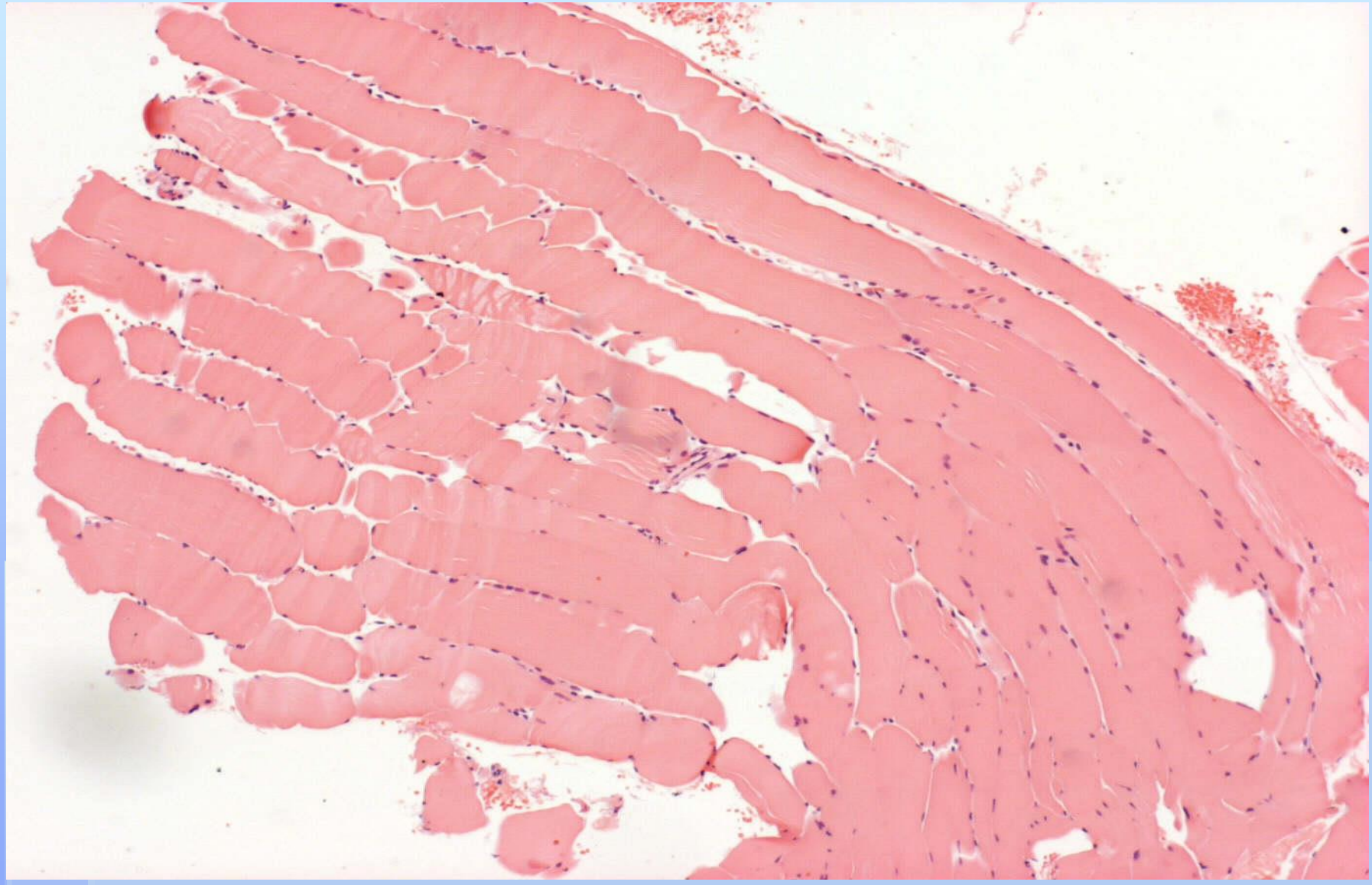
Fracture site 3



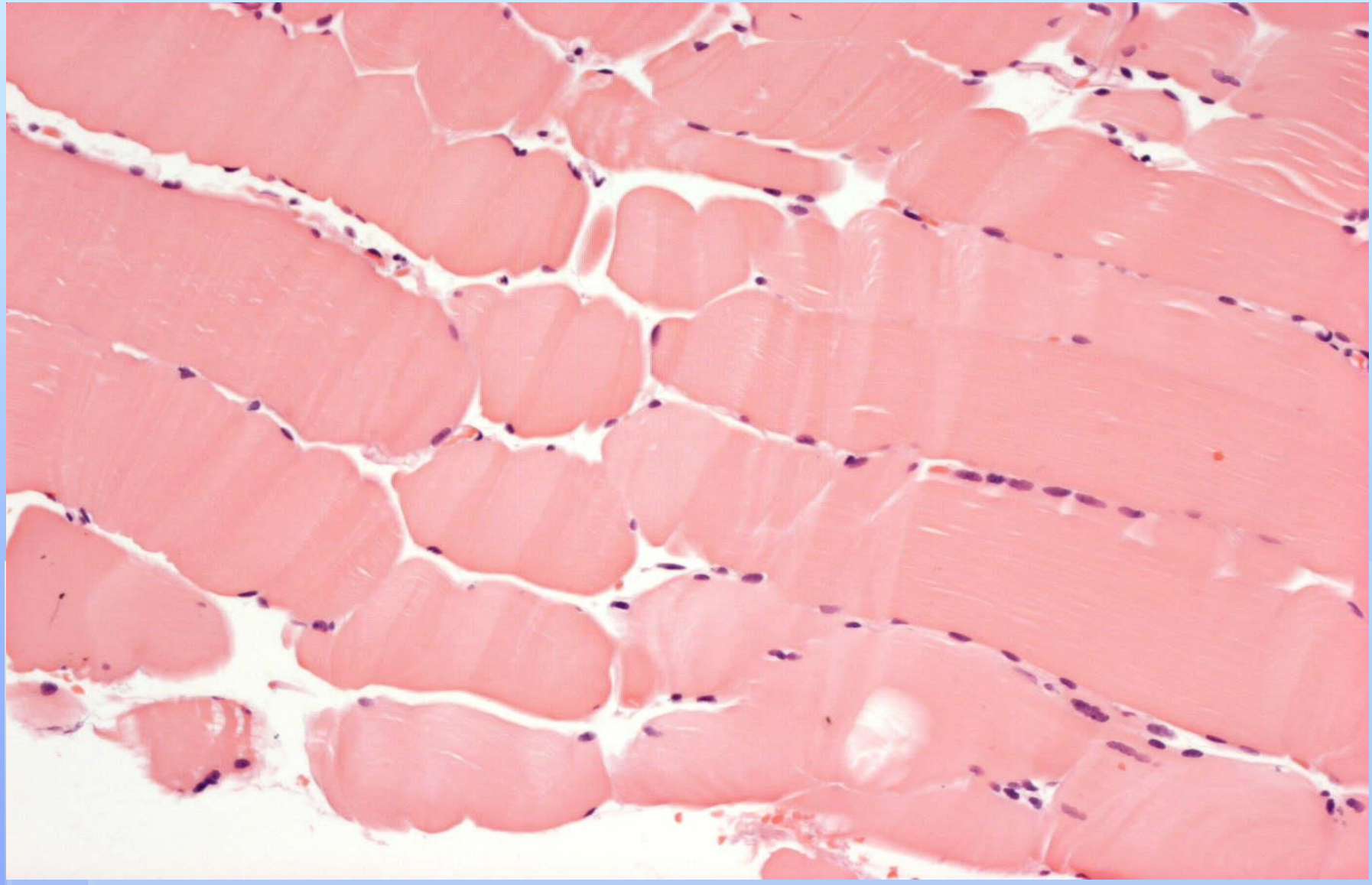
Muscle biopsy 1



Muscle biopsy 2



Muscle biopsy 3



November 2003

- Discharged
- 2 weeks later subcutaneous oedema re-accumulated and readmitted to hospital
- No DVT found by dopplers.
- Given methylprednisolone
- Developed obstructive uropathy causing ARF
  - Bladder catheter and double nephrostomy tubes inserted
  - MRSA at nephrostomy sites

December 2003

- Samples sent to Salisbury to look for

  FIPILI – PDGFR A fusion gene results were negative

  - Blood stored for future reference should more targets be identified

- **Commenced on Imatinib on 10th Dec. 200 mg once / day**

January 2004

- Overall improvement in general condition initially lasted few weeks with improved oedema and counts.

- Began to feel unwell
  - Increased swelling of right thigh
  - parasthesia of scrotum
- Imatinib dose was reconsidered
  - ? Not enough
  - ? Too much

February 2004

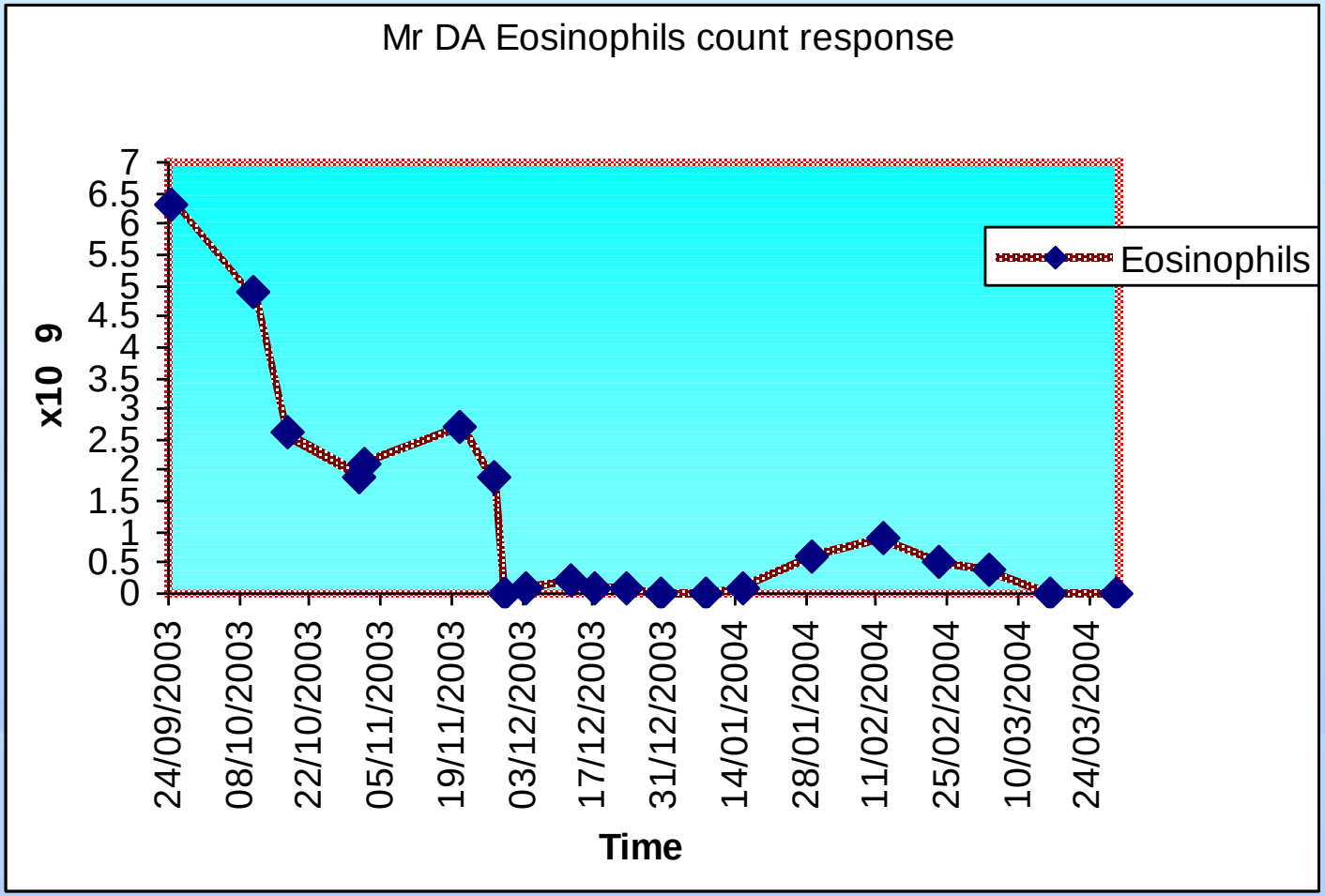
- Seen by Prof. J. Apperley at Hammersmith Hospital London :
  - Trial of higher dose of Imatinib (400mg)
  - If not fully controlled may need to add in Hydroxyurea
  - Suggested Bone Marrow sample in 2-3 months to assess progress

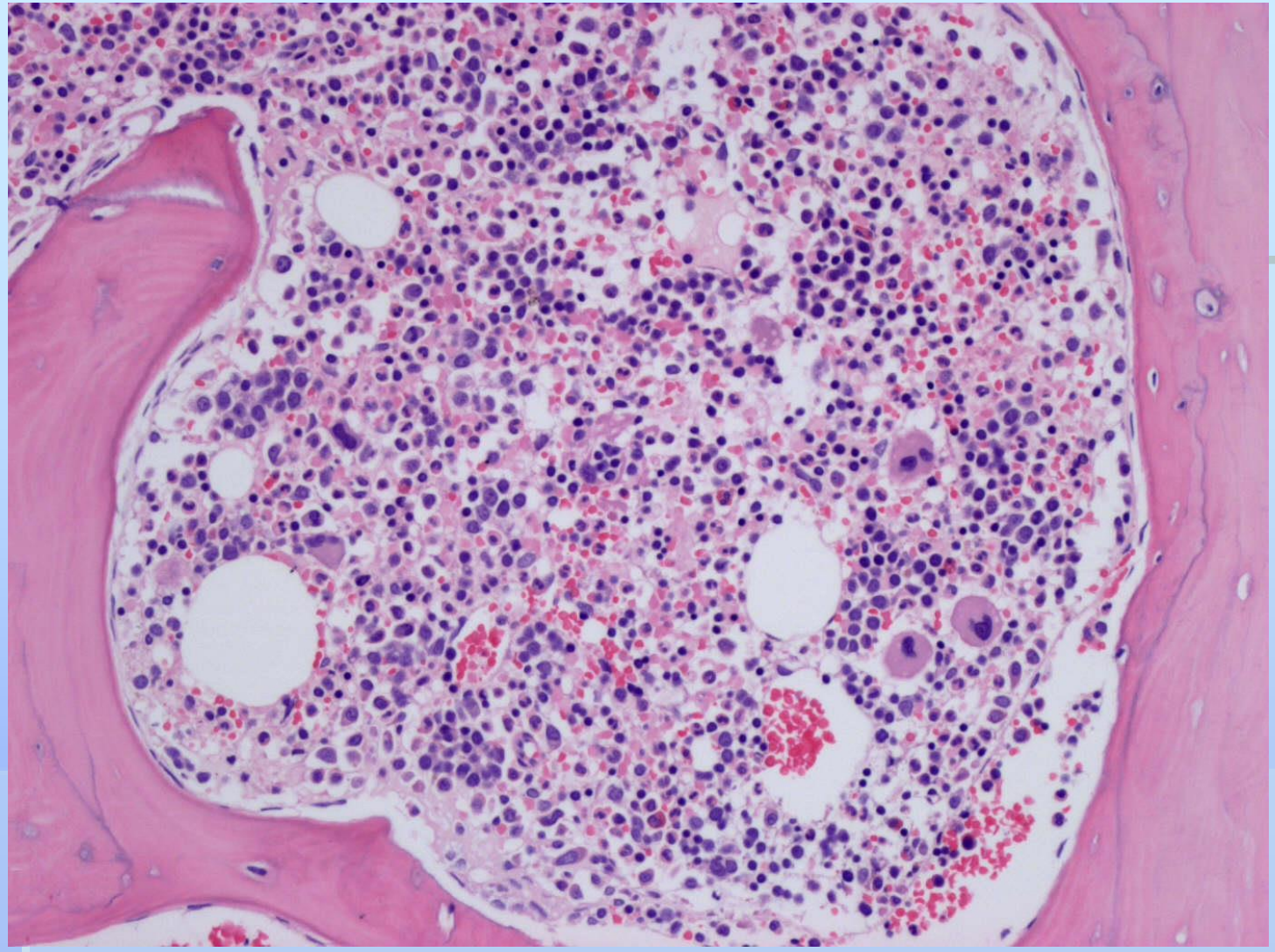
March 2004

- Worsening pains and moderate swelling 2 weeks after increasing Imatinib dose.
- Pain not helped by diclofenac
- Imatinib dose reduced to 200mg , Hydroxyurea added.

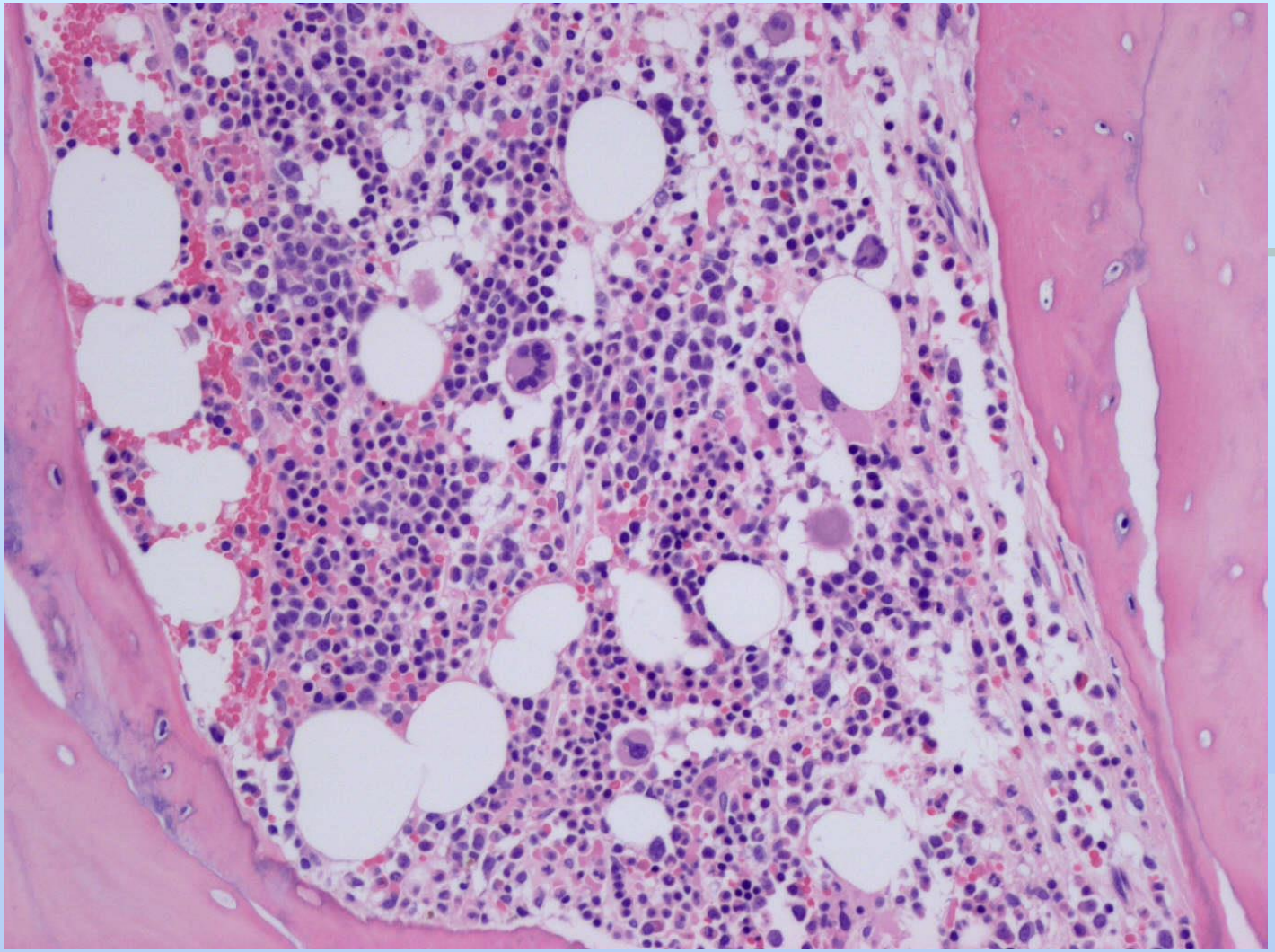
April 2004

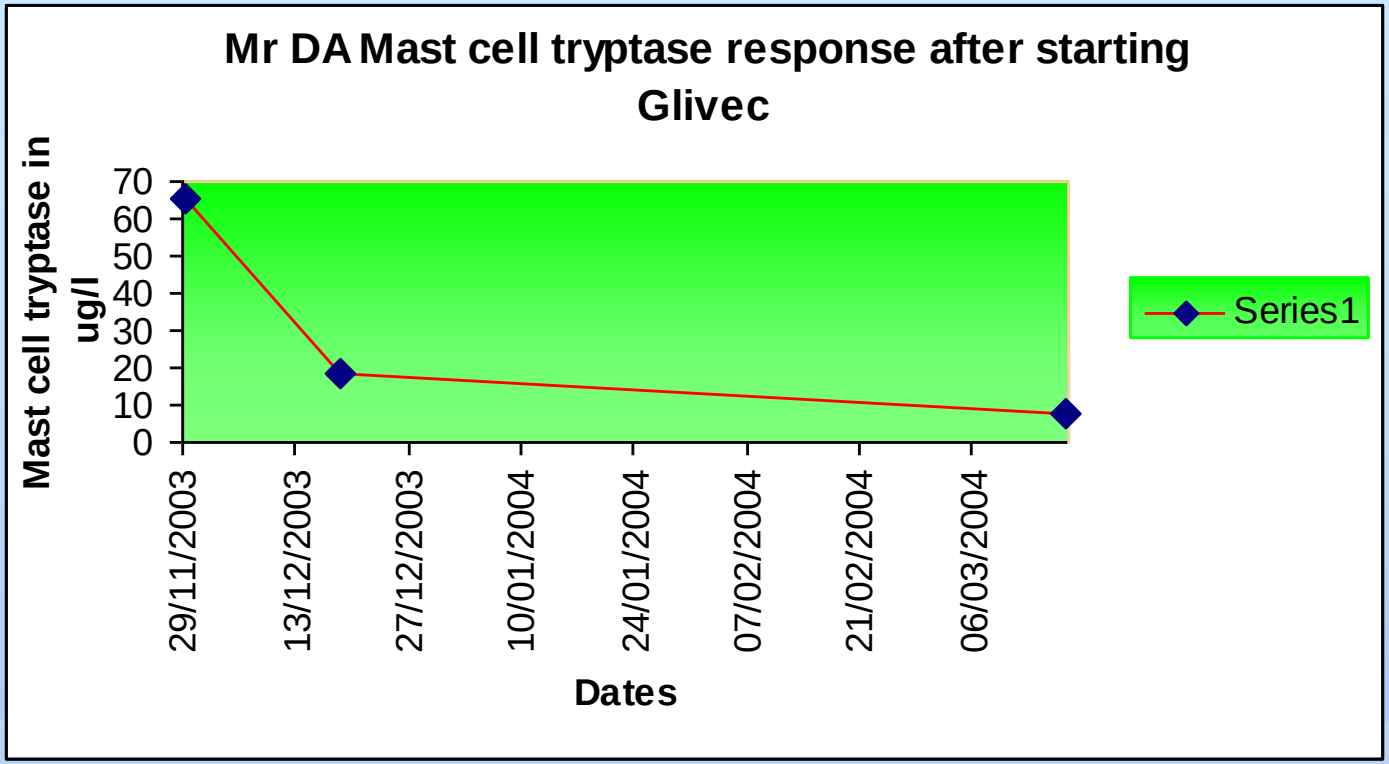
- Admitted with pain Rt leg and Rt foot drop
- Nerve conduction studies confirm nerve compression in the mid/lower thigh.
- Given analgesia, Gabapentin , Amitryptyline and Prednisolone 20 mg.
- No new swelling, groin swelling disappeared for the first time. Blood parameters continue to improve.


Mr DA Eosinophils count response
x10 9
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
24/09/2003
08/10/2003
22/10/2003
05/11/2003
19/11/2003
03/12/2003
17/12/2003
31/12/2003
14/01/2004
28/01/2004
11/02/2004
25/02/2004
10/03/2004
24/03/2004
Time
Eosinophils



Repeat BM Trephine after 4 months on Glivec, Note reduced eosinophils, Megakaryocyte clustering and abnormal bone texture




Mr DA Mast cell tryptase response after starting Glivec
Mast cell tryptase in ug/l
70
60
50
40
30
20
10
0
29/11/2003
13/12/2003
27/12/2003
10/01/2004
24/01/2004
07/02/2004
21/02/2004
06/03/2004
Dates
Series1

Now an in patient

Worsening swelling in both legs more on the right.
Gained 2 stones in weight over 3 weeks.
Infammed Rt medial thigh ? Infection CRP 44
Neutropenia
Falling Hb

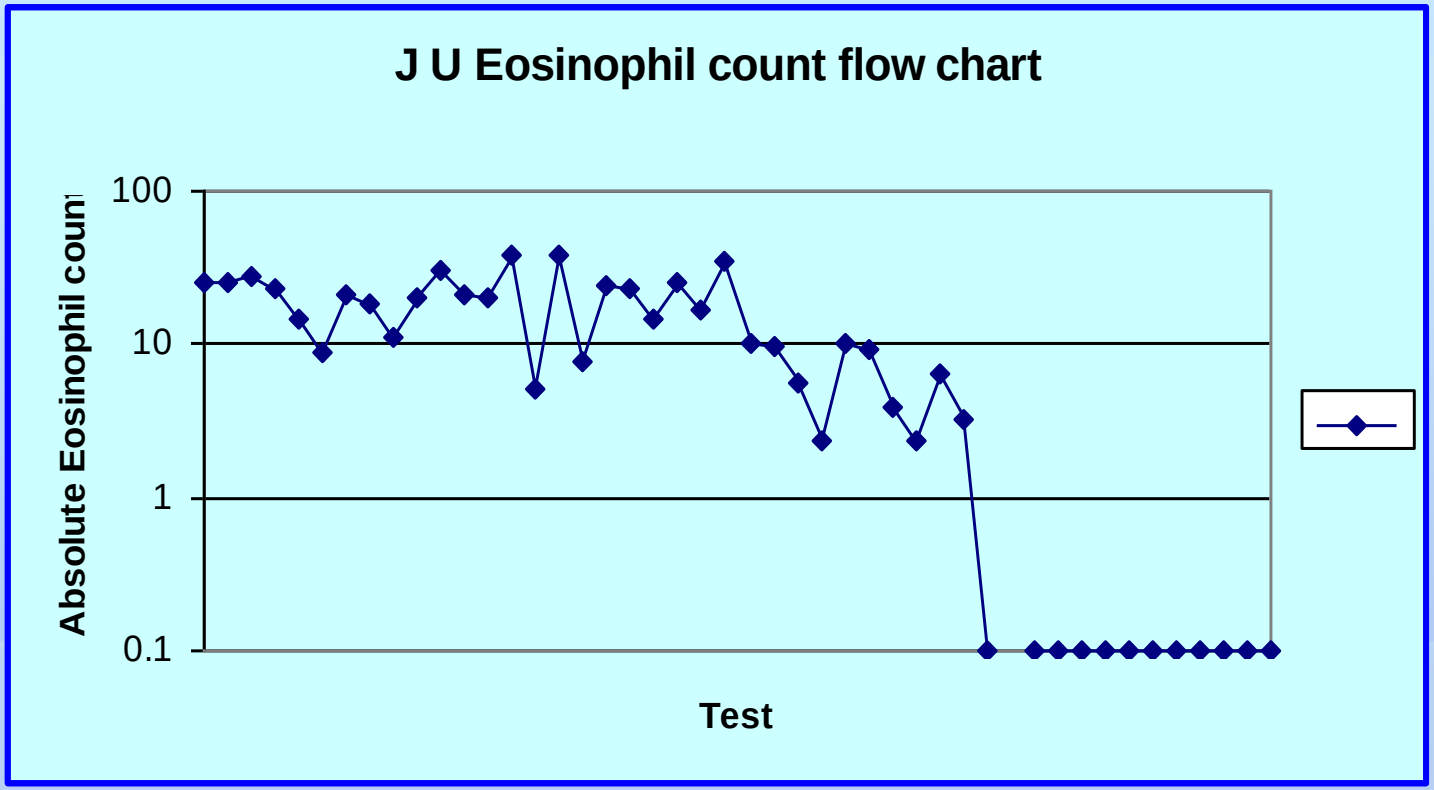
Stop Hydroxyurea and Amitryptyline.

Supportive management
Furosemide
Methyl prednisolone
FFP given.

Patient -2

- **July 2000**
  - Persistent non purulent productive cough previous 6 months.
  - Persistent eosinophilia.
  - Weight loss of 3 stones over 18 months.
  - Severe night sweats and pruritus after warm bath.
  - No wheeze**.**
- **Examination:**
  - Splenomegaly at 2 cms below costal margin.
- **Blood count : Hb 129 WBCs 37.9 N 6.0 Eosin 25.4 Plts 213**
  - ESR 25 CRP < 6 LDH 685 Polyclonal increase in Igs.
- **Bone marrow :**
  - Aspirate :Hypercellular with marked excess of eosinophils.
  - Trephine : No increase in reticulin, prominent eosinophils , consistent with myeloproliferative disorder.
  - Cytogenetics : 46XY No other abnormality.

- **Biochemistry:**
  - ANA , rheumatoid factor . ANCA Negative
  - Aspergillus fumigatus precipitins Negative , Sputum cultures Neg No AAFB
- **Echocardiography :**
  - EF of 60% , No myocardial infiltration or speckling
- **Clinical course:**
  - No response to Prednisolone 40 mg /day , changed to Hydroxyurea.
  - Hydroxyurea caused cytopenias Low Hb and Low Plts
  - Deteriorating slowly , persistent symptoms, required blood transfusion Oct 2002 , also developed hepatomegaly with signs of CCF (Rt) mostly.
  - Progressive splenomegaly.
  - A short course of interferon could not be tolerated.
  - Vincristine injections once every 2 weeks (2 injections)
  - Referred To J Apperley at the Hammersmith / London considered for Glivec trial 28/11/2002
  - Started at 400 mg marked symptomatic improvement noted from the first two weeks.


J U Eosinophil count flow chart
Absolute Eosinophil count
100
10
1
0.1
Test

Normal eosinophil count varies between 0.1 to 0.6

Causes of Eosinophilia

Mild Eosinophilia (0.7-1.5 X 10^9/L)

- Allergic rhinitis
- Drug reaction
- Parasitic disease
- Neoplasms
- Radiation therapy
- Certain infectious diseases
- Gastrointestinal disease
- Hay fever or atopy
- Extrinsic asthma
- Occupational lung disease
- Skin disease
- Immunodeficiency state
- Long-term dialysis

Moderate Eosinophilia (1.5-5 X 10^9/L)

- Parasitic disease
- Drug reaction
- Pulmonary eosinophilia syndrome
- Other connective tissue disorders
- Intrinsic asthma
- Polyarteritis nodosa
- Neoplasms
- Hypereosinophilic syndrome

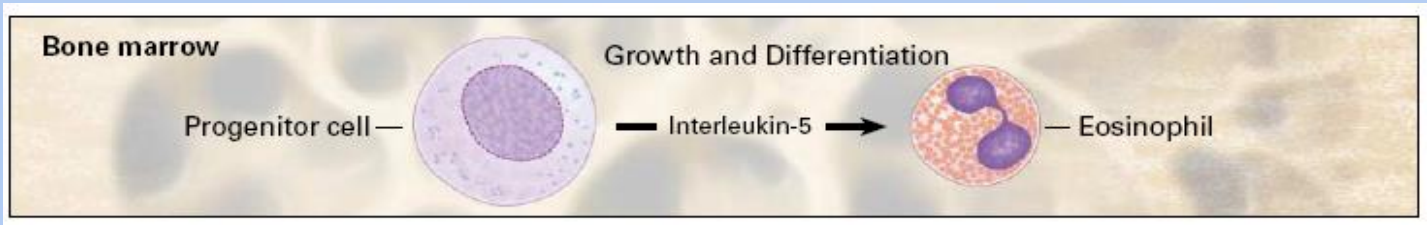
Marked Eosinophilia (>5 X 10^9/L)

Parasitic diseases

- Visceral larva migrans associated with *Toxocara canis* or *Toxocara cati* infestation
- Tissue migration during larval stage (eg, ascaris, trichina, hookworm, *Strongyloides*)
- Trichinosis, hookworm infection, ascariasis, strongyloidiasis

Hypereosinophilic syndrome
Eosinophilic leukemia Disorder usually associated with moderate eosinophilia

Neoplasms
Polyarteritis nodosa
Drug reaction



Hyper Eosinophilic Syndrome (HES)

- Eosinophil count of more than 1.5 $x10^9/\mu l$.
- Persistent more than 6 months.
- No cause identified (Parasitic , drugs , allergy, lymphoma,…).
- Signs and symptoms of organ damage.
- Absence of clonality

WHO classification of myeloid disorders

HES and Chronic Eosinophilic Leukaemia (CEL) are grouped together :

(It may be virtually impossible to distinguish between clonal eosinophilia and eosinophilia secondary to abnormal cytokine production for which no etiologic basis is recognized . The diagnosis of CEL or HES can be made only after a number of infectious, inflammatory, and neoplastic diseases known to be associated with eosinophilia have been excluded).

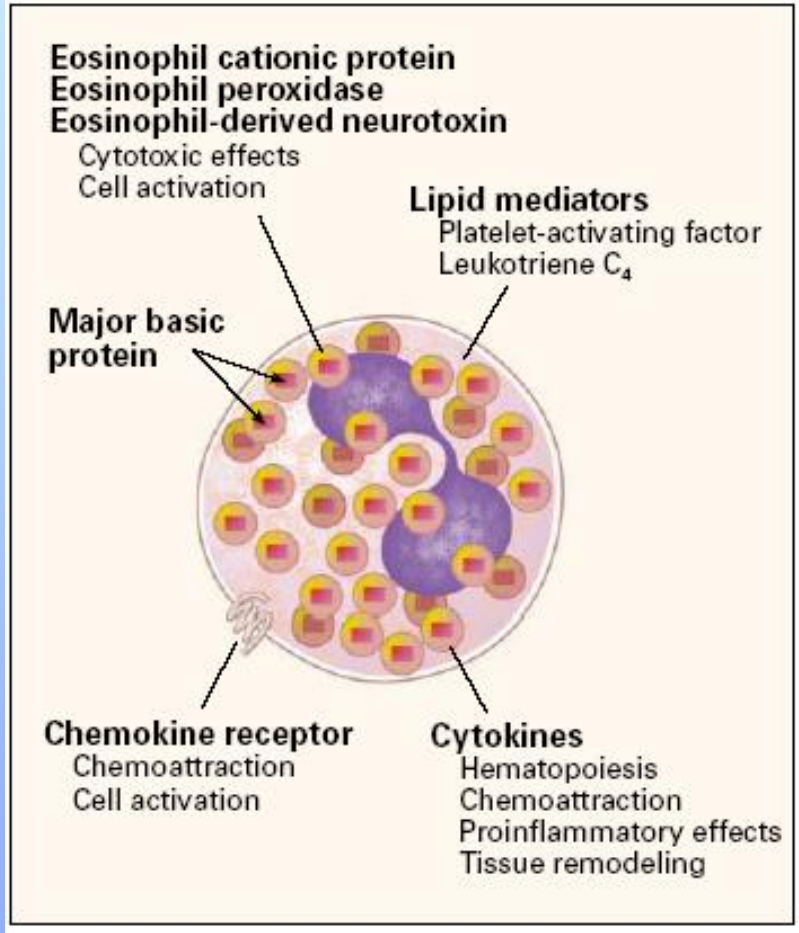
TABLE 4. BIOLOGIC FEATURES OF EOSINOPHILS.*

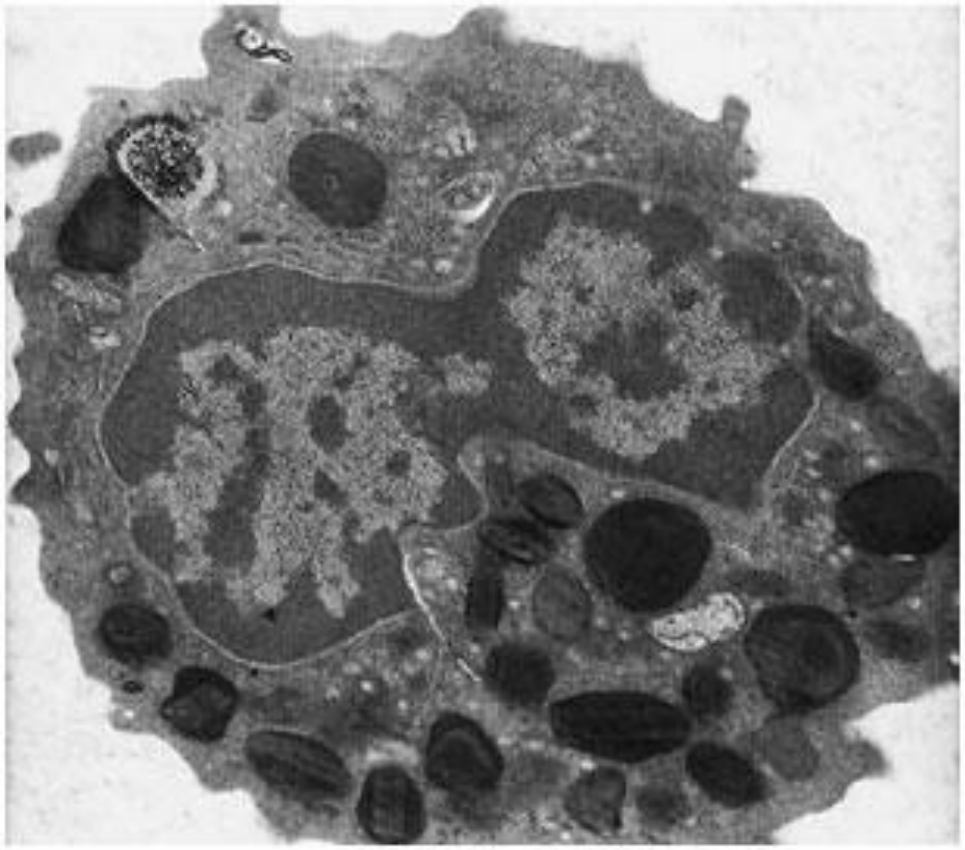
Characteristics
Bilobular nuclei
Large acidophilic granules
Eosinophilic cytokines
Granulocyte–macrophage colony-stimulating factor
Interleukins 3 and 5†
Cytokines released by eosinophils
Interleukins 1, 3, 4, 5, 6, and 8
Tumor necrosis factor α
Transforming growth factor α and β
Major inhibitory protein 1a
Granulocyte–macrophage colony-stimulating factor
Granule contents
Small, lysosomal granules
Phagocyte oxidase proteins, which generate superoxide
Large, eosinophilic granules
Eosinophilic peroxidase
Major basic protein
Eosinophilic cationic protein
Eosinophil-derived neurotoxin

*Adapted from Boyce with the permission of the publisher.[6]

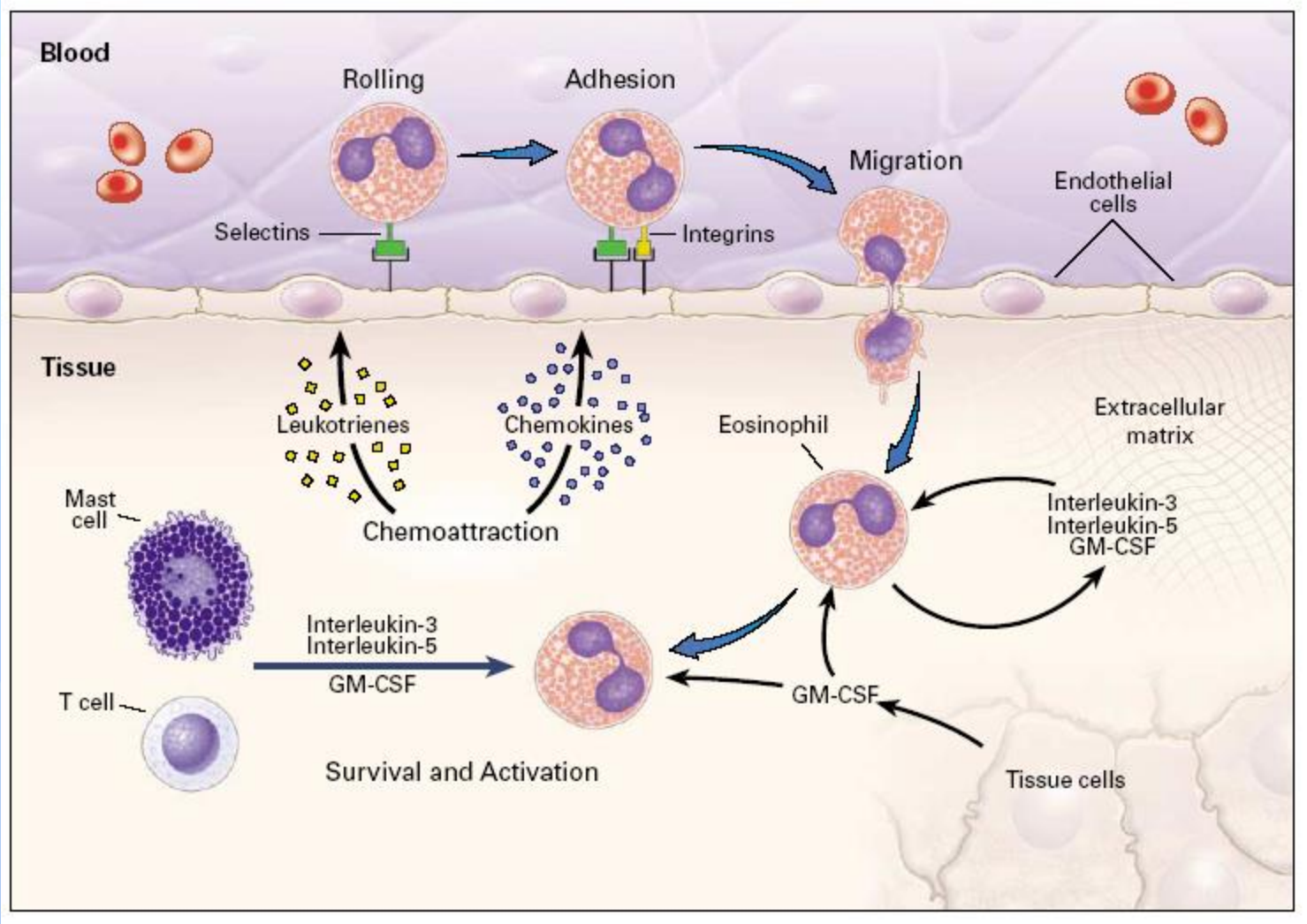
†The activity of interleukin-5 is most specific for eosinophils.

Ultrastructure of the Eosinophil





Functions of Eosinophils



Unusual features in case -1

- Osteolytic lesions with areas of bone necrosis , resulting in pathologic fracture.
- Increased thickness of bony trabeculae in trephine samples.

Bone Disease in Hyper eosinophilia

(Altamirano AC, Rodríguez DD
Fracturas lumbares en un paciente con síndrome hipereosinofílico idiopático
***Cir Ciruj* 1999; 67(3): 108-111.)**

Lumbar fractures in a patient with idiopathic hypereosinophilic syndrome

Symptoms of Hyper eosinophilia

System	Patients	Manifestations
Constitutional	≅ 50%	Weakness, fatigue, anorexia, fever, weight loss, myalgias
Cardiopulmonary	> 70%	Cough, dyspnea, heart failure, arrhythmias, endomyocardial disease, pulmonary infiltrates, pleural effusions, emboli
Hematologic	> 50%	Thromboembolic phenomena, anemia, thrombocytopenia, lymphadenopathy, splenomegaly
Neurologic	> 50%	Altered behavior and cognitive function, spasticity, peripheral neuropathy, focal cerebral lesions
Dermatologic	> 50%	Dermatographism, angioedema, rashes, pruritus
Gastrointestinal	> 40%	Diarrhea, nausea, abdominal cramps
Immunologic	≅ 40%	Elevated immunoglobulins (especially IgE), circulating immune complexes

Management of persistent Eosinophilia

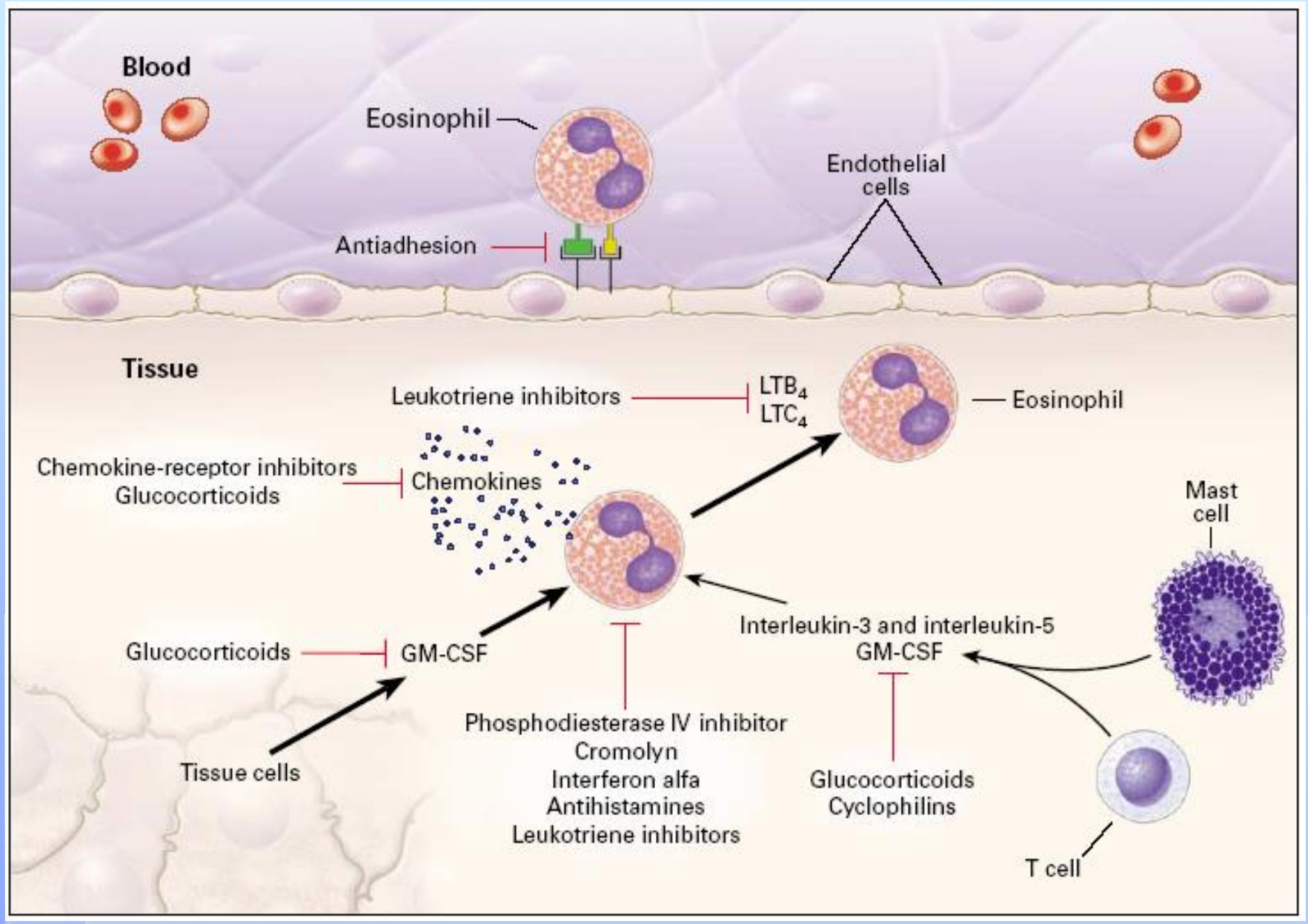
Things to consider

1- Search for a clonal bone marrow disorder.

2- Search for organ damage

- No treatment If mild and no organ damage
- Steroids (Prednisolone , pulse methyl prednisolone
- Hydroxyurea (Hydroxycarbamide)
- Vincristine
- Other treatments

Drug treatment of Eosinophilia



Interferon

(IFN) has been shown to produce benefit in steroid-resistant cases
At a dose of 1.5 to 8 MU/day

Annals of Internal Medicine

November 1994 | Volume 121 Issue 9 | Pages 648-653

Interferon-Alpha Treatment of Six Patients with the Idiopathic Hypereosinophilic Syndrome

Joseph Butterfield and Gerald Gleich

New modalities of treatment

Imatininb

First used in 2001

The NEW ENGLAND JOURNAL of MEDICINE

Volume 348:1201-1214 March 27, 2003 Number 13

A Tyrosine Kinase Created by Fusion of the *PDGFRA* and *FIP1L1* Genes as a Therapeutic Target of Imatinib in Idiopathic Hypereosinophilic Syndrome

Jan Cools, Ph.D., Daniel J. DeAngelo, M.D., Ph.D., Jason Gotlib, M.D., Elizabeth H. Stover, M.Phil., Robert D. Legare, M.D., et al

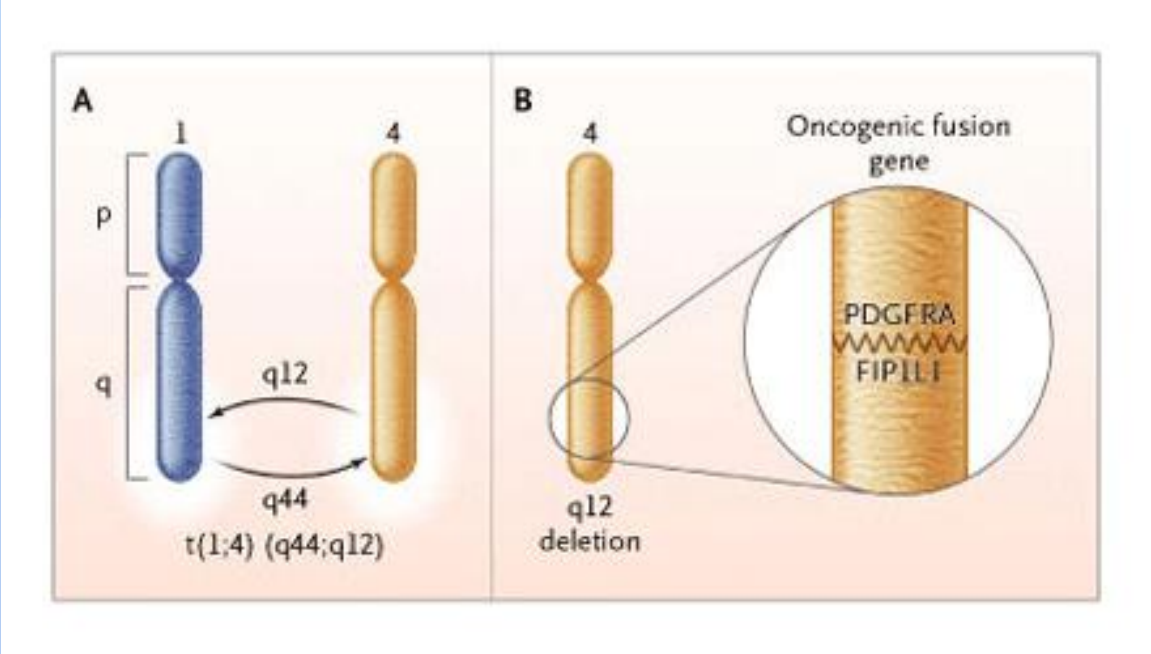
Nine of the 11 patients treated with imatinib had responses lasting more than three months in which the eosinophil count returned to normal.

Fip1-like 1 (*FIP1L1*) gene to the PDGFR (*PDGFRA*)

- A fusion gene is created by the del(4)(q12q12),
- 800-kb deletion on chromosome 4q12 (Figure 2).
- The deletionis not visible using standard cytogenetic banding techniques and explains why most HES patients with the fusion have an apparently normal karyotype.

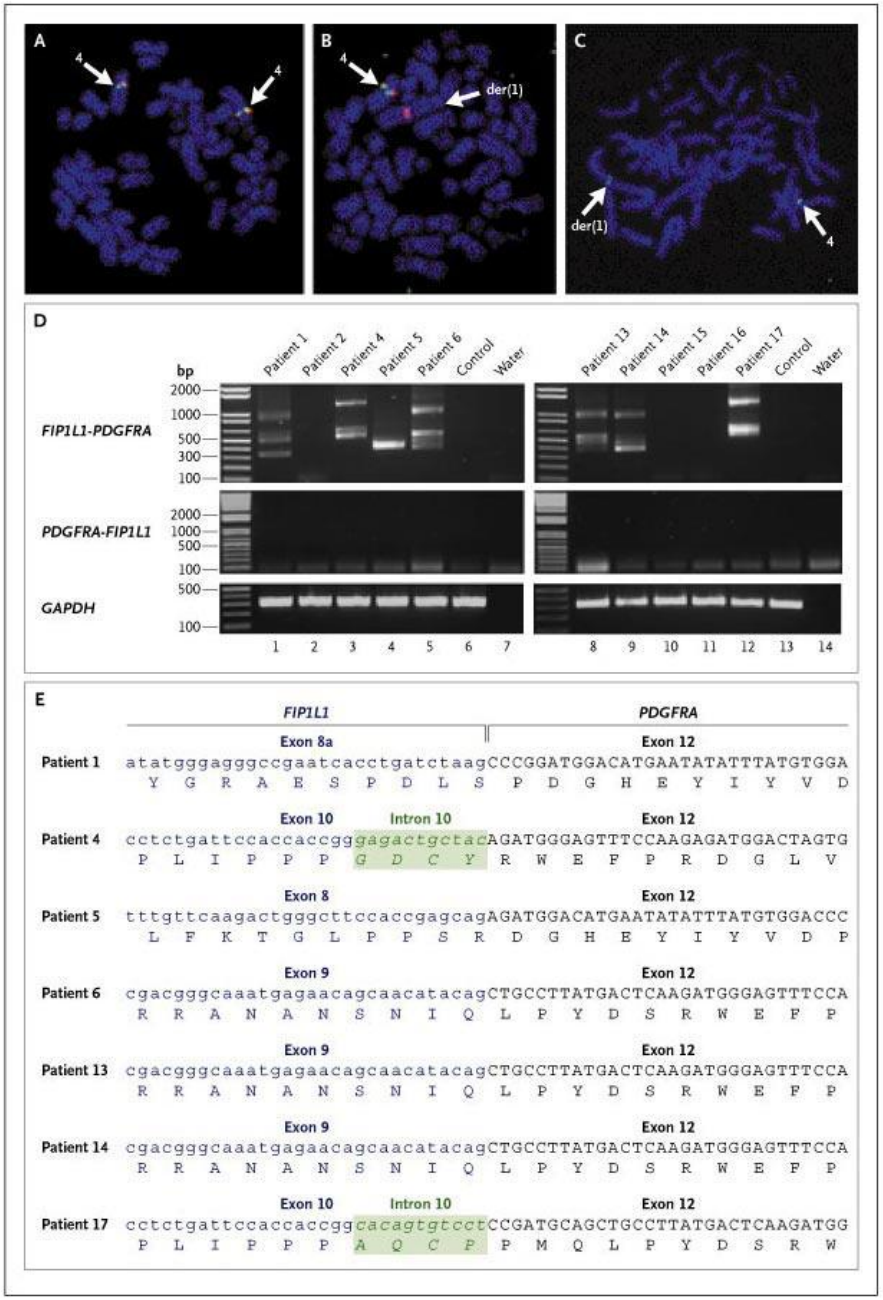
The gene generated by an interstitial deletion on chromosome 4q12.

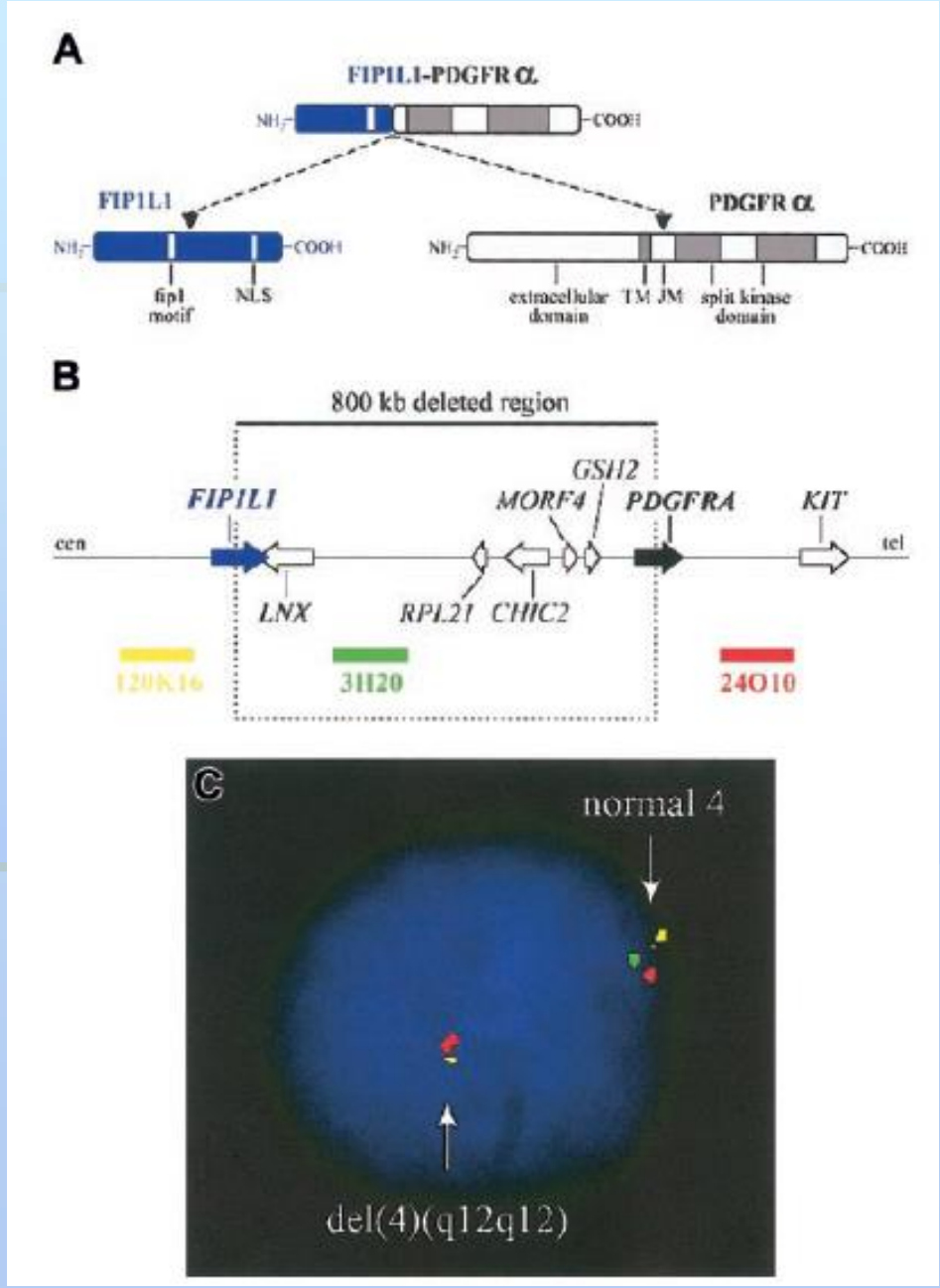
FIP1L1-PDGFR is a constitutively activated tyrosine kinase that transforms hematopoietic cells and is inhibited by imatinib



FISH appearance of the

FIP1L1/PDGFRA gene




A
FIP1L1-PDGFR α
NH2
COOH
FIP1L1
PDGFR α
fip1 motif
NLS
extracellular domain
TM
JM
split kinase domain
B
800 kb deleted region
GSH2
FIP1L1
MORF4
PDGFRA
KIT
cen
tel
LNX
RPL21
CHIC2
120K16
31I20
24O10
C
normal 4
del(4)(q12q12)

blood JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

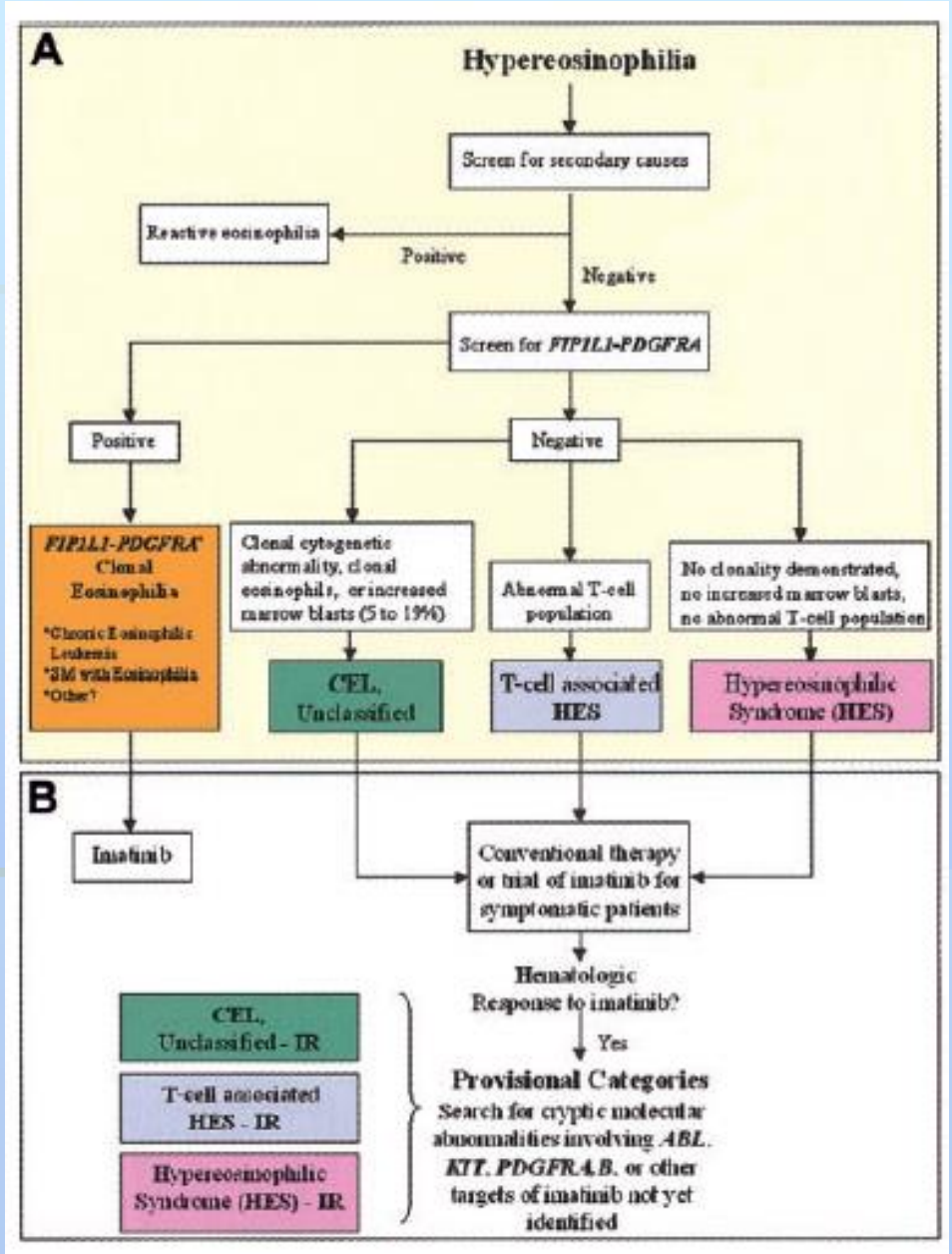
2004 103: 2879-2891

The FIP1L1-PDGFR fusion tyrosine kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia: implications for diagnosis, classification, and management

Jason Gotlib, Jan Cools,,,, D. Gary Gilliland, and Steven E. Coutre

- **The FIP1L1-PDGFR fusion proteintransforms hematopoietic cells, and its kinase activity is inhibited by imatinib at a cellular 50% inhibitory concentration (IC50) 100-fold lower than BCR-ABL**
- **It may be useful to consider the implications of the *FIP1L1- PDGFRA* fusion within a recently proposed framework that classifies blood eosinophilia as reactive, clonal, and HES.**

Proposed classification Of hypereosinophilia In view of the FIP1L1/ PDGFRA



Interleukin -5

Abnormal Clones of T Cells Producing Interleukin-5 in Idiopathic Eosinophilia

Hans-Uwe Simon, M.D., Sabine Gisela Plötz, M.D., Reinhard Dummer, M.D., and Kurt Blaser, Ph.D.

Volume 341:1112-1120 October 7, 1999 Number

Volume 349:2334-2339 December 11, 2003 Number 24

Use of an Anti–Interleukin-5 Antibody in the Hypereosinophilic Syndrome with Eosinophilic Dermatitis

Sabine-Gisela Plötz, M.D., …,and Johannes Ring, M.D.

- **Imatinib can be effective in patients with the syndrome who have normal or increased serum concentrations of interleukin-5.**
- **Those who have clonal T cells and polymorphous skin lesions — interleukin-5 does seem to have a critical role.**