



Specialty conference, USCAP San Diego
Pulmonary Pathology
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Case n°3

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ERI 3 INSERM¹

MESONAT Registry²

MESOPATH Group³



Inserm

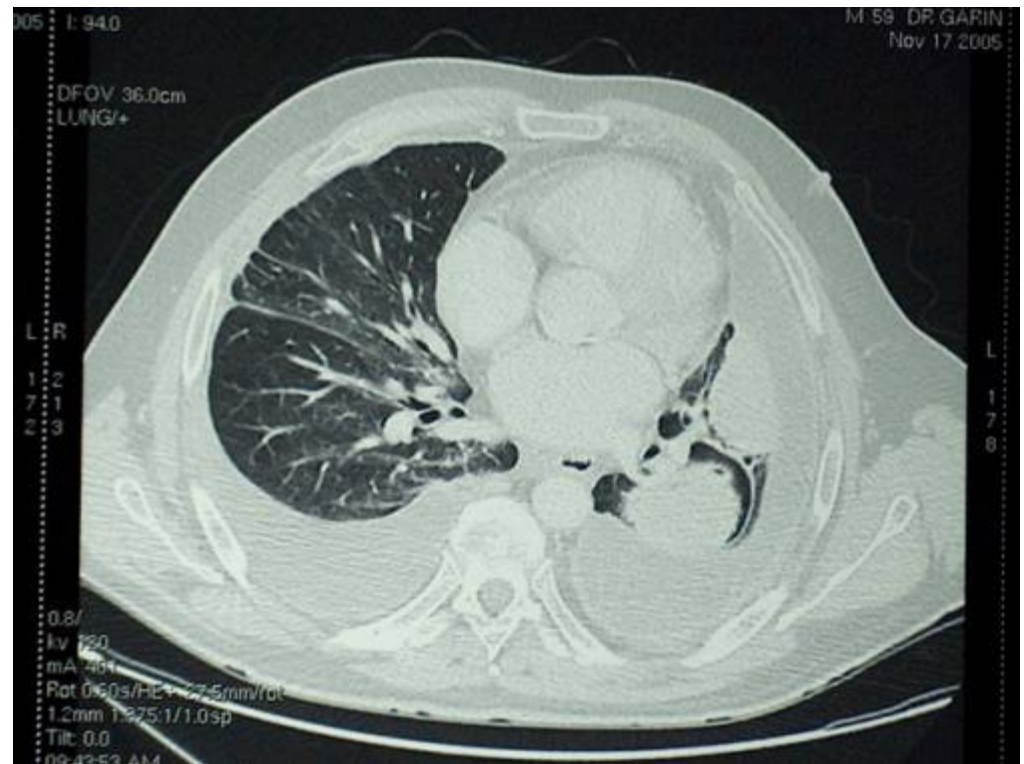
Institut national
de la santé et de la recherche médicale

Clinical summary

- ✿ A 59-year-old white man, a storekeeper in a car factory from 1965 to 2000.
- ✿ Was hospitalized for a bilateral pleural effusion
- ✿ And a 3 months history of increasing dyspnea, cough, and fatigue.
- ✿ He also complained of fever, drenching night sweats and progressive body weight loss (8kg).
- ✿ At the time of admission asbestos exposure has ceased 5 years earlier.

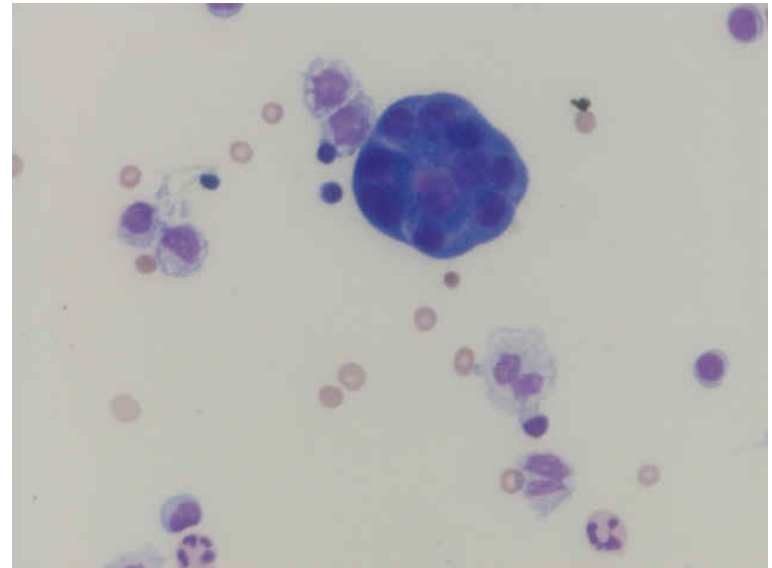
Clinical summary

- The patient had a previous history of:
 - systemic hypertension treated by hydrochlorothiazide
 - and Parkinson's disease diagnosed and treated by Celance® (pergolide) since 1998 1mg daily.
- The CT Scan confirmed bilateral pleural effusions
 - Diffuse bilateral pleural thickening
 - Rounded atelectasis



Laboratory data

- ❖ Normal WBC count with
 - ❖ 21% lymphocytes
 - ❖ Proteins:73g/L
 - ❖ C reactive protein:138mg/L
 - ❖ Sedimentation rate [ESR]:107mm/hr
 - ❖ LDH:652
- ❖ Thoracocentesis disclosed
 - ❖ lymphocytic and bloody fluid
 - ❖ Protein 39g/L
 - ❖ Normal Adenosine desaminase activity
 - ❖ No evidence of malignancy on cytology



Histopathologic findings

Representative slide is from the pleurectomy

- The pleural thickening ranged from 0.1 to 0.3 cm, and the pleura was white and firm



Histopathologic findings

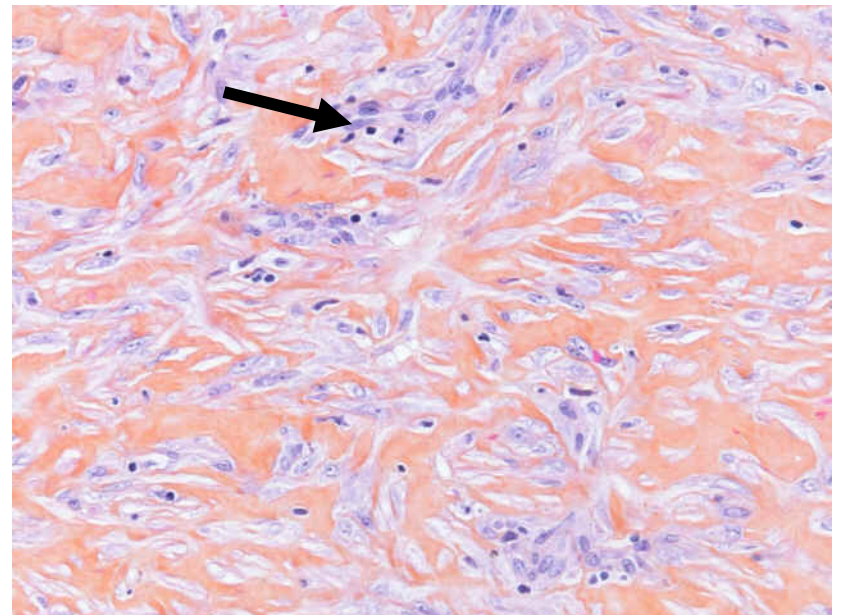
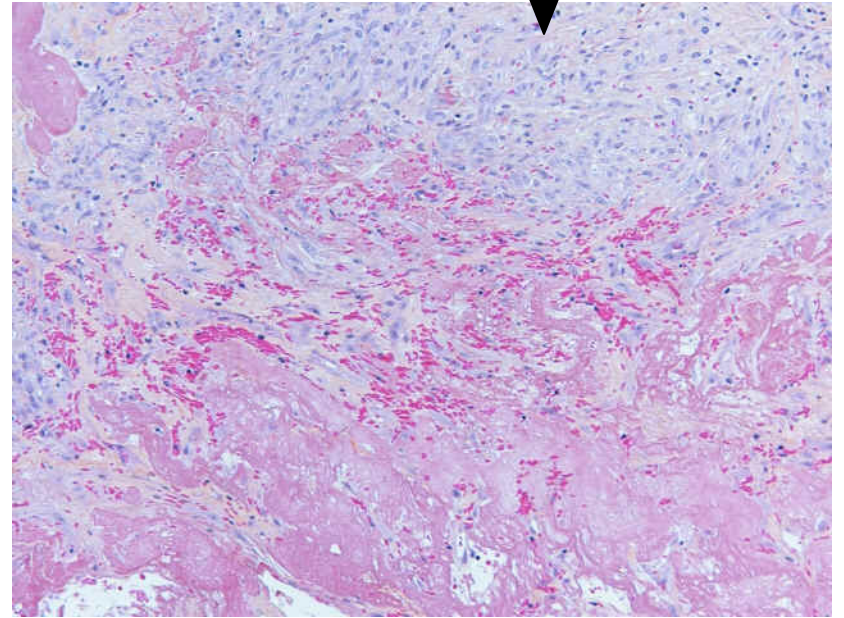
H&E stained sections of the pleura showed:

- severe diffuse thickened and fibrotic pleura
- With serofibrinous exudate at the surface
- And diffuse cellularity with fibrosis and inflammatory cells.



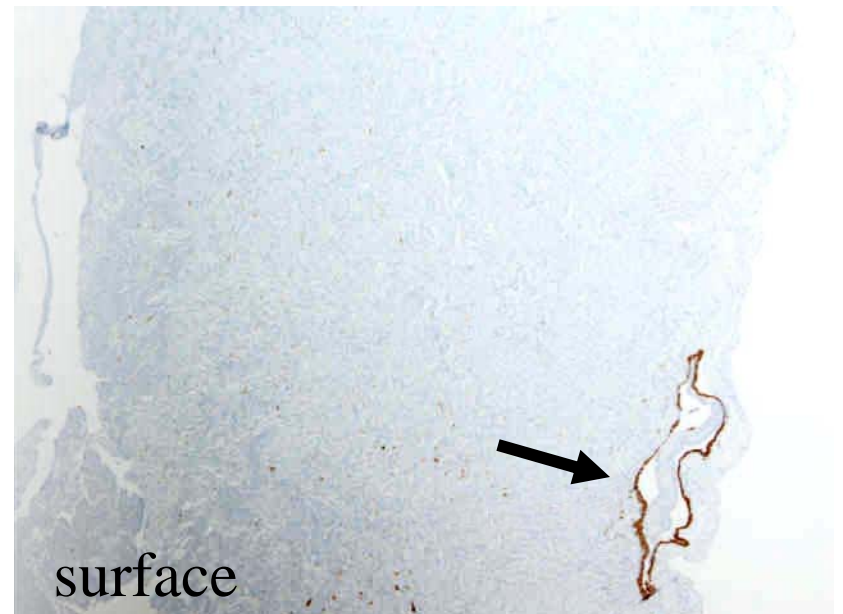
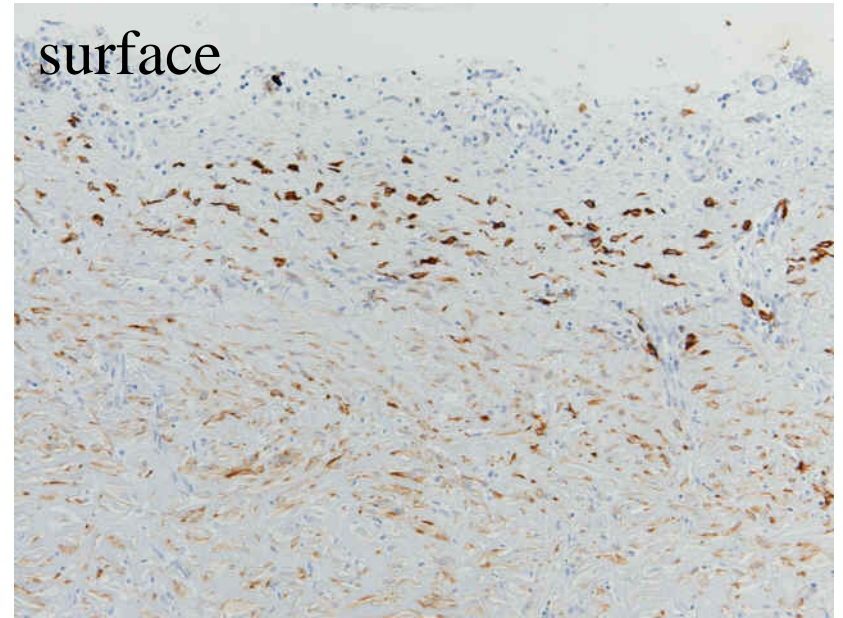
Histopathologic findings

- At higher magnification
 - acute fibrinous pleuritis
- Cellularity was greater beneath the pleural surface
- Some plump, atypical fibroblasts were deeply seated with few mitosis



Histopathologic findings

- At higher magnification
 - Ipx with AE1/3 showed positive cells under effusion
 - the spindle cells deeply seated within the areas of fibrosis were also positive and parallel the surface mesothelium.
 - Sequestration of mesothelial cells (↓)



Panelists' Diagnoses Case 3

- Organizing fibrous pleuritis ? drug induced
- Acute fibrinous and chronic fibrous pleuritis, favor drug-induced injury
- Reactive pleural fibrosis ? Drug reaction
- Reactive pleural fibrosis ? Drug related

Diagnosis

Pergolide-induced fibrous pleuritis
in a patient with asbestos exposure

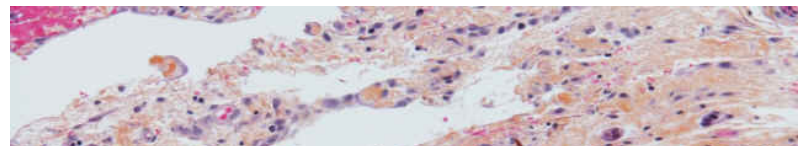
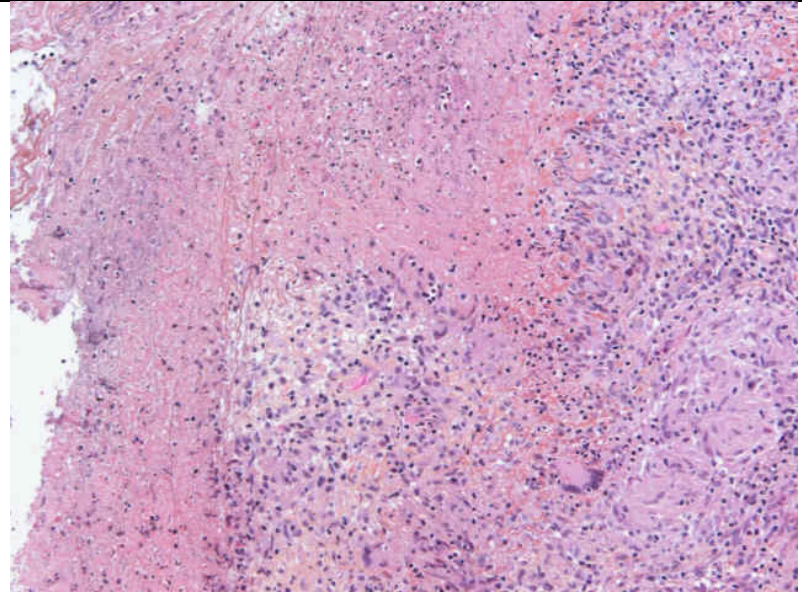
Discussion

- ✿ The differential diagnosis included
 - ✿ Infection (tuberculosis)
 - ✿ Malignancy
 - ✿ Any other causes of recurrent exudative pleuritis
 - ✿ Benign asbestos related pleural effusion/fibrosis
 - ✿ Drug reactions

Infection /Tuberculosis

Clinical manifestations were suspicious for tuberculosis

- ✿ In tuberculosis, effusions are usually unilateral and massive
- ✿ associated with post-primary tuberculosis involving the apices of the upper lobes
- ✿ pleural fluid profile shows:
 - ✿ lymphocytic effusion,



- The diagnosis was excluded in view of:
 - the absence of necrotizing granulomas on serial recuts
 - negative findings with multiple cultures

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Discussion

Churg et al, Am J Surg Pathol, 2000; 24:1183-1200

Cagle and Churg, Arch Pathol Lab Med, 2005, 129:1421-7

Churg et al, covered the diagnostic criteria for the separation of benign from malignant mesothelial proliferations

Benign mesothelial reactions

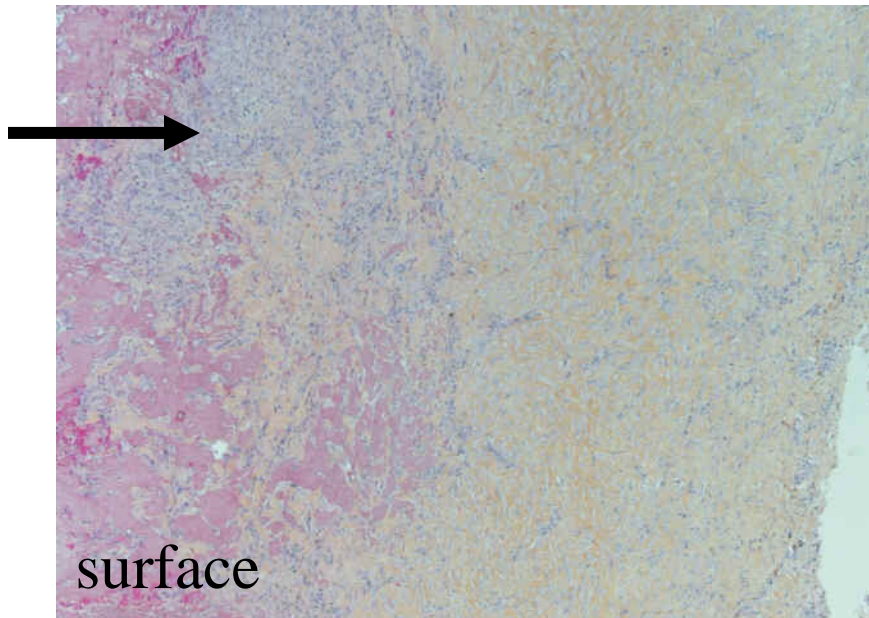
- Zonation (higher cellularity under effusion)
- No true invasion of the parietal fat
- Storiform pattern absent or minimal
- Cytologic atypia beneath the surface
- Elongated capillaries perpendicular to the surface
- Mitoses may be present
- Necrosis usually absent

Desmoplastic mesothelioma

- No zonation (cellularity away from effusion)
- True invasion of the parietal fat
- Storiform pattern usually present
- Cytologic atypia present or absent in any area
- Capillaries haphazardly distributed and inconspicuous
- Many mesotheliomas show few mitoses
- Bland necrosis

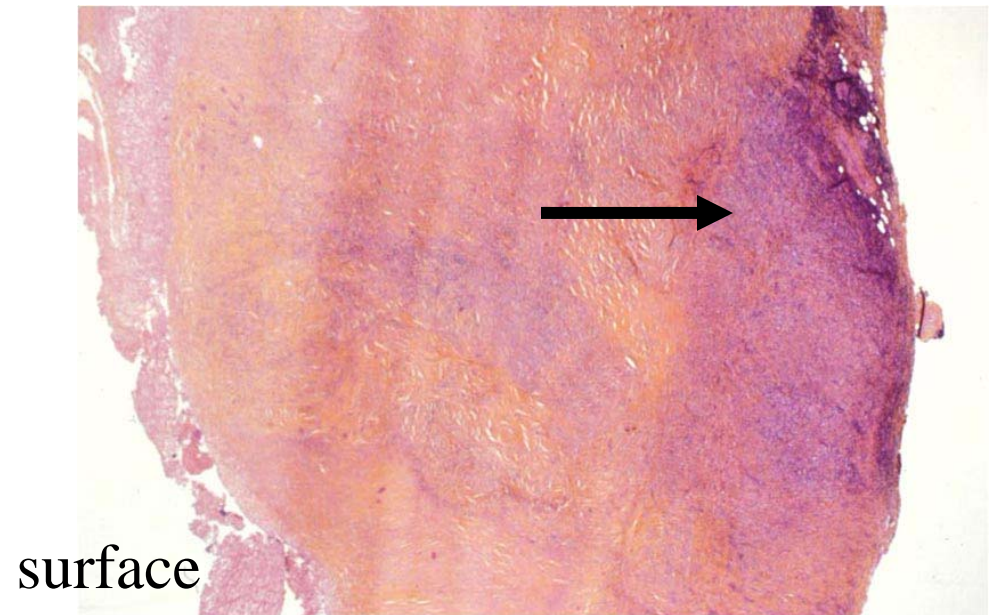
Discussion

❖ Fibrous pleuritis



- ❖ Zonation (higher cellularity under effusion)
- ❖ Storiform pattern absent or minimal
- ❖ Absence of bland necrosis

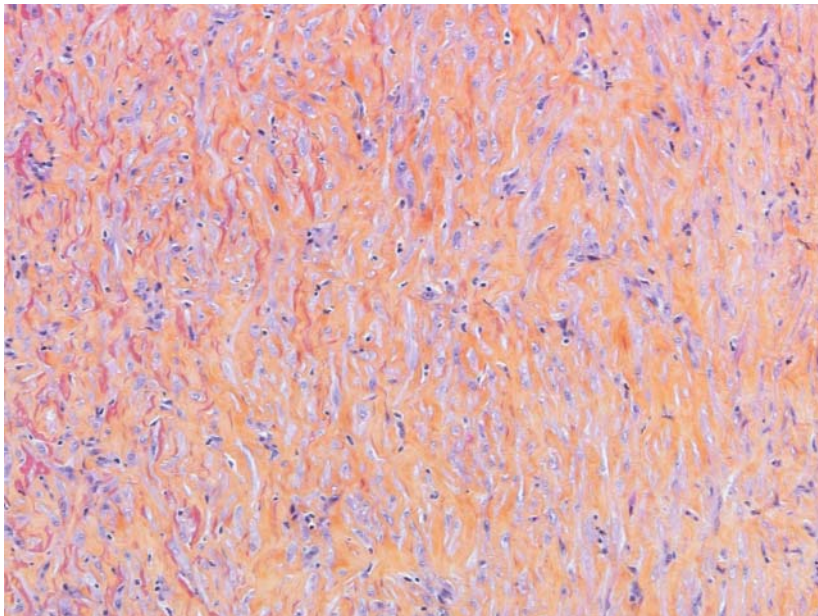
❖ Desmoplastic mesothelioma



- ❖ No zonation (cellularity away from effusion)
- ❖ Storiform pattern present
- ❖ Bland necrosis

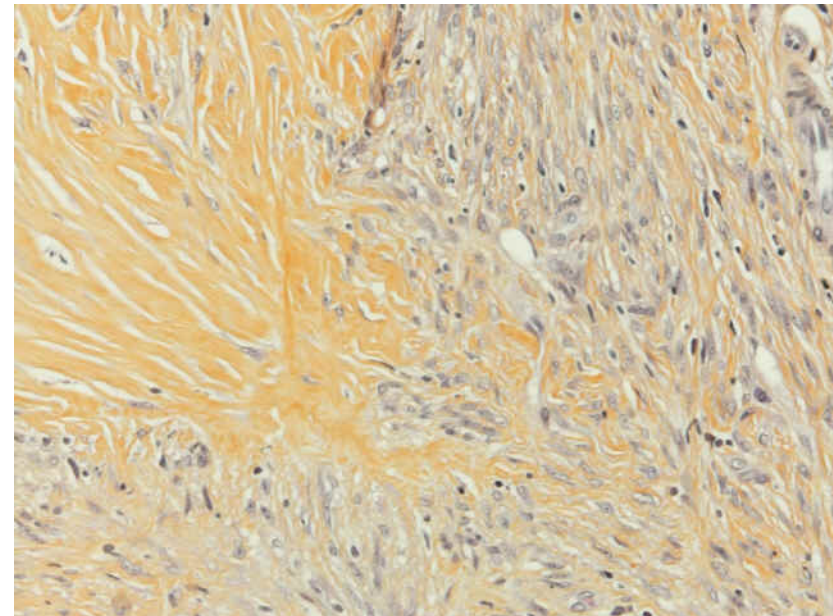
Discussion

❖ Fibrous pleuritis



Spindle cells are oriented parallel to the surface mesothelium

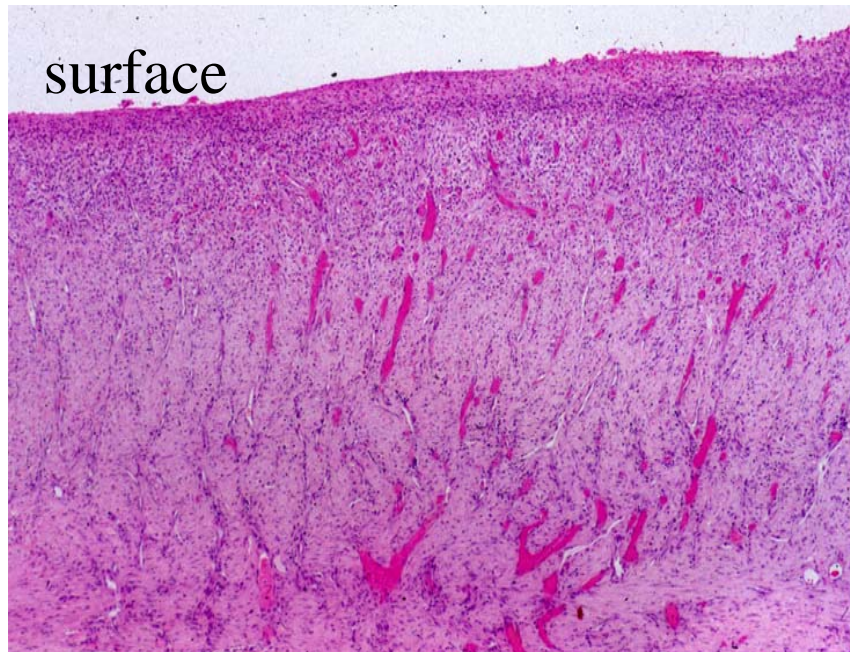
❖ Desmoplastic mesothelioma



Abrupt and haphazard transition in cellularity is one of the most useful clues favoring malignancy

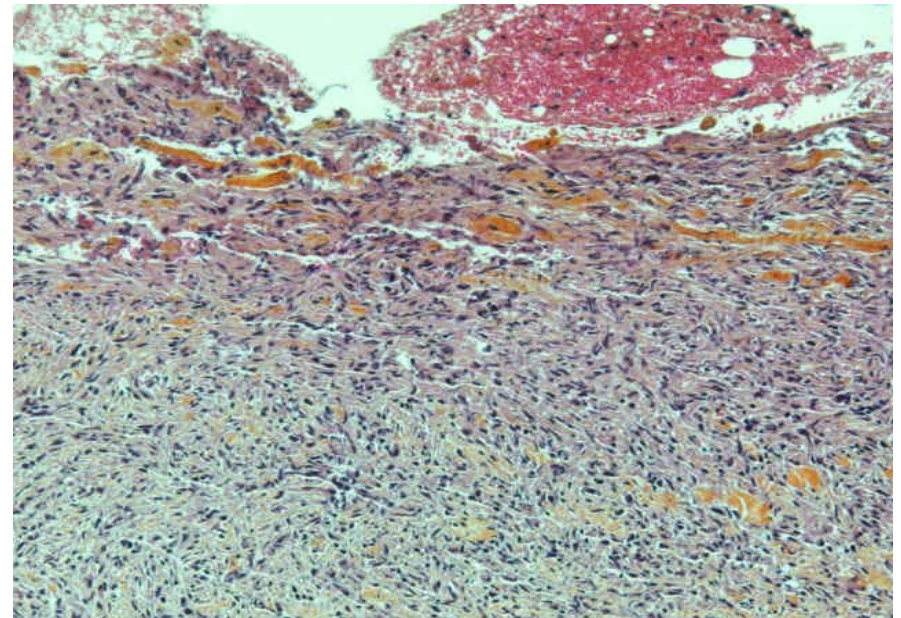
Discussion

✿ Fibrous pleuritis



✿ Elongated capillaries perpendicular to the surface.

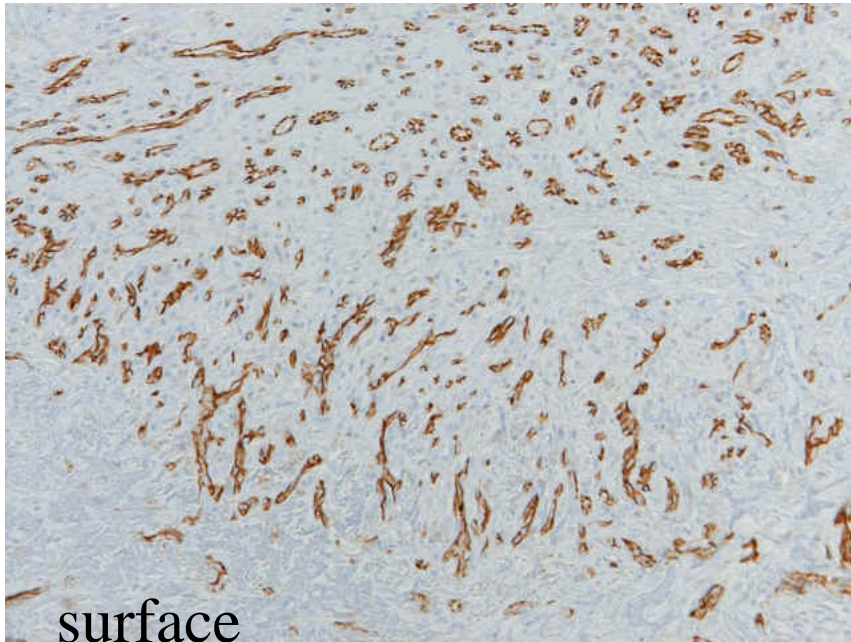
✿ Desmoplastic mesothelioma



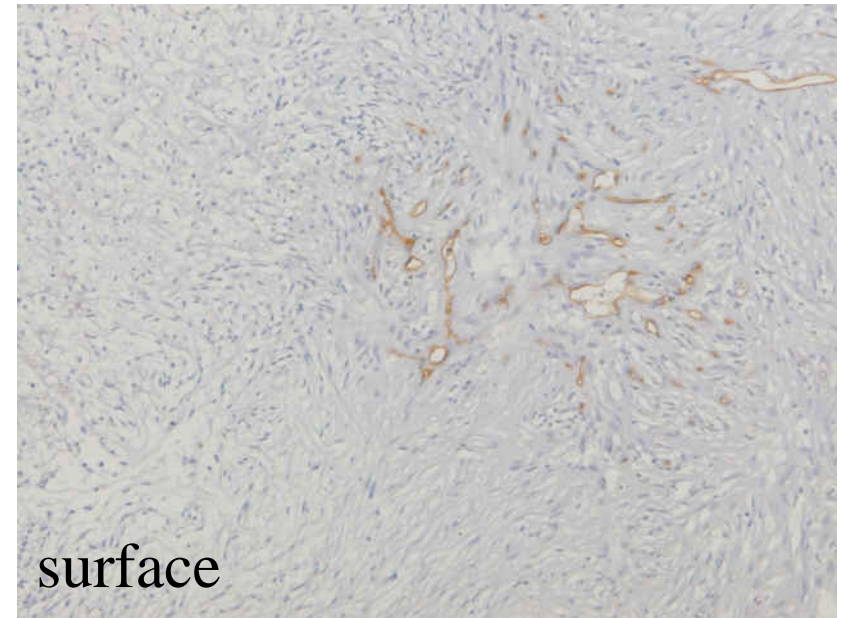
✿ Capillaries haphazardly distributed and inconspicuous.

Discussion

■ Fibrous pleuritis



■ Desmoplastic mesothelioma



■ Elongated capillaries perpendicular to the surface

■ Capillaries haphazardly distributed and inconspicuous.

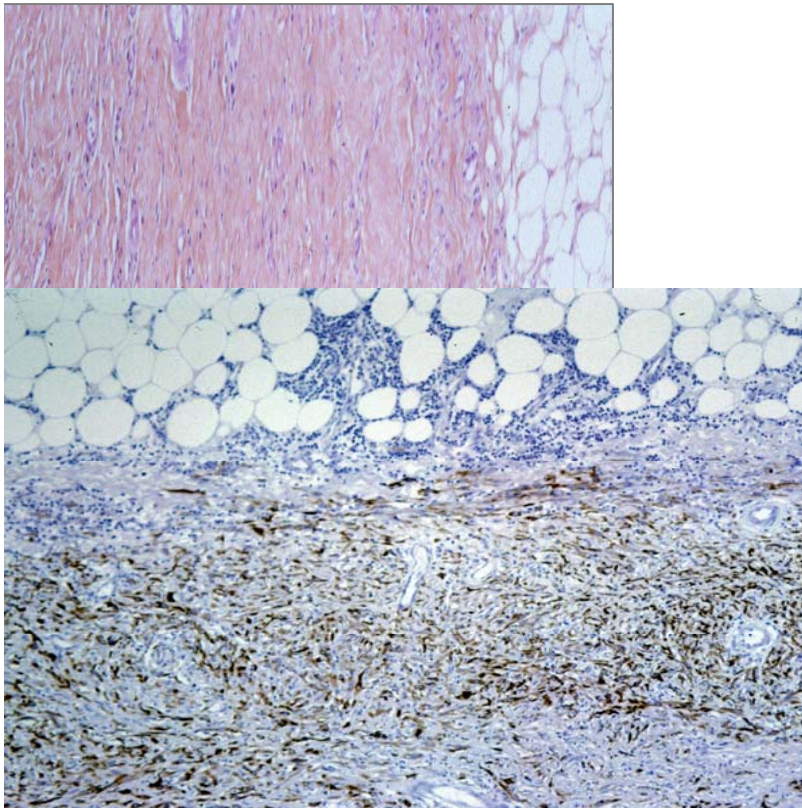
Discussion

Cagle et al, Hum Pathol, 1994

Mayall et al, J Pathol, 1992

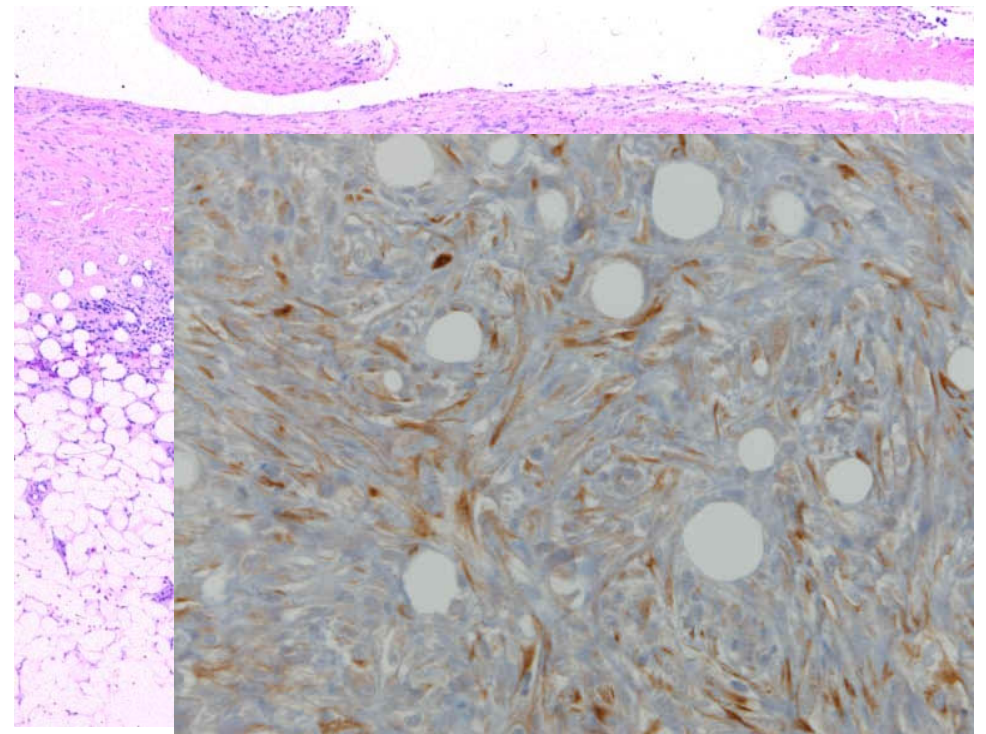
Cury et al, J Pathol, 1999

❖ Fibrous pleuritis



❖ Ipx: CK's , p53 and EMA may be positive

❖ Desmoplastic mesothelioma



❖ Ipx: CK's highlight genuine fat invasion, p53 and EMA usually positive but not diagnostic

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 - ✿ Benign asbestos related pleural effusion/fibrosis
 - ✿ Drug reactions

Causes of pleural fibrosis

- ❖ Diffuse visceral and parietal fibrosis
 - ❖ Recurrent exudative effusion
 - ❖ Asbestos exposure
 - ❖ Collagen-vascular disease
 - ❖ Drug reactions
- ❖ Fibrothorax
- ❖ Pleural fibrosis secondary to renal disease
- ❖ Pleural fibrosis secondary to infections
- ❖ Pleural fibrosis secondary to trauma
- ❖ Pleural fibrosis secondary to asbestos

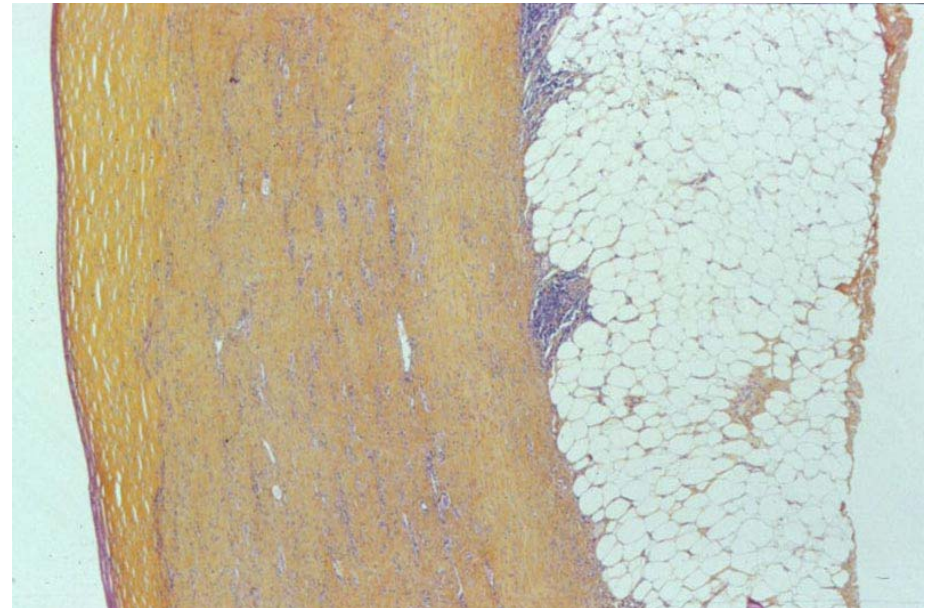
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Benign asbestos related pleural lesions

Churg et al, in Occupational Disorders of the Lung. Saunders

- ❖ Asbestos may cause acute pleurisy (5%)
- ❖ may recur on the same side or more commonly on the contralateral side after interval of months or years.
- ❖ Risk increase with the dose of asbestos
- ❖ Diffuse pleural fibrosis
 - ❖ This disorder usually involves the visceral pleura (parietal).
 - ❖ Is believed to follow benign asbestos effusion
 - ❖ Diffuse pleural fibrosis is usually unilateral but may be bilateral



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 - ✿ Infection (tuberculosis)
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Drug induced pleural disease

- ❖ Drug-associated pleural effusion, pleuritis, and /or pleural thickening is an uncommon event compared to drug-induced parenchymal lung disease.
- ❖ Often misdiagnosed
- ❖ Drug effects are believed to be causal:
 - ❖ When exposure induces pleural disease
 - ❖ When the pleural response remits on discontinuation of the drug
 - ❖ And when the pleural disease recurs with re-exposure to the same drug

Drug induced pleural disease

- ✿ The first description of pleural adverse effects was made by Cooper et al, in 1986
- ✿ Drug induced pleural disease in **PUBMED**- 1176 -references

Drug induced pleural fibrosis

adapted from Morlock et al, Chest 1999

❁ Cardiovascular agents

- ❁ Amiodarone
- ❁ Minoxidil
- ❁ Practolol

❁ Ergoline drugs

- ❁ Bromocriptine
- ❁ Methysergide
- ❁ Pergolide

❁ Sclerotherapeutic agents

❁ Drug induced lupus-like pleuritis

- ❁ Procainamide
- ❁ Hydralazine
- ❁ Other drugs

❁ Pleural fluid eosinophilia

- ❁ Nitrofurantoin
- ❁ Dantrolene
- ❁ Valproic acid
- ❁ Propylthiouracil
- ❁ Isotretinoin

❁ Chemotherapeutic agents

- ❁ Bleomycin
- ❁ Mitomycin
- ❁ Procarbazine
- ❁ Methotrexate
- ❁ Cyclophosphamide

❁ Other agents

- ❁ Acyclovir
- ❁ Clozapine
- ❁ D-penicillamine
- ❁ Granulocyte stimulating factor
- ❁ Interleukin-2
- ❁ Itraconazole
- ❁ L-Tryptophan
- ❁ Simvastatin

Pathogenic mechanisms

- ✿ Hypersensitivity or allergic reactions
- ✿ Direct toxic effect
- ✿ Increased free radical production
- ✿ Suppression of anti-oxidant defenses
- ✿ Chemical-induced inflammation

Pergolide

McElvaney et al Arch Intern Med, 1988

Danoff et al, Chest 2001

Huggins et al, Clin Chest Med , 2004

Hillerdal et al , Eur Respir J, 1997

Knoop et al, Eur Respir J, 1997

Brooks, JNNP, 2000

Tintner et al, Archiv Neurol, 2005

✿ Pergolide is an ergot-derived dopamine agonist used in:

✿ Parkinson's disease

✿ Restless legs syndrome

✿ Has been reported to cause pleuro-peritoneal and retroperitoneal fibrosis.

Pergolide

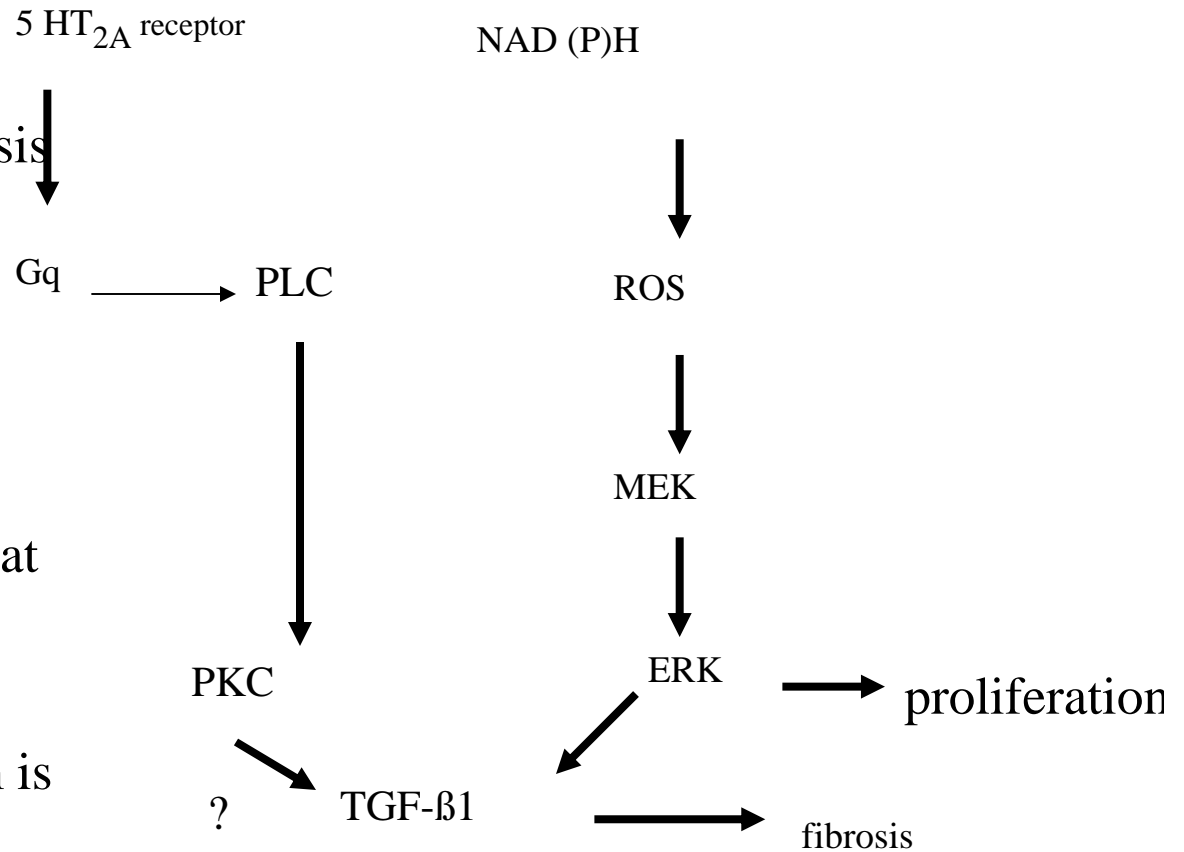
Tintner et al, Arch Neurol, 2005

Grewal et al, Am J Physiol, 1999

✿ The mechanisms by which the ergot derivatives produce fibrosis remains obscure

✿ May represents a serotonergic effect of this medication as serotonin is known to cause fibrosis (ergots are antagonists at serotonin receptors)

✿ Immunopathogenic mechanism is another possibility



Signaling cascade from 5 HT_{2A} receptor to TGF-β1

Adapted from Tintner et al, 2005

Pergolide induced pleural reaction

- ❖ A pergolide –induced fibrous pleuritis should be considered in a patient presenting with :
 - ❖ Bilateral pleural disease
 - ❖ Frequently associated with a systemic illness including fever, weight loss, and acute inflammatory syndrome
- ❖ Pergolide-induced pleural fibrosis usually occurs within 3 years of initiation of treatment.
- ❖ Is probably enhanced by asbestos exposure.

Conclusion

- ❖ A thorough work up to determine the cause (s) of pleural effusion in a patient taking pergolide is not only of academic or medico-legal interest but also of practical therapeutic importance to prevent at the early stage fibrosing complications.
- ❖ It is recommended not to use ergot-derivatives such as pergolide in Parkinson's disease in patients exposed to asbestos.
- ❖ Nowadays, the association of asbestos and Pergolide- induced pleural fibrosis does not seem fortuitous

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