GRAND ROUNDS CLINICI DEL MERCOLEDÌ
con il Policlinico San Matteo

Sistema Socio Sanitario
Regione Lombardia

Fondazione IRCCS Policlinico San Matteo

ATS Pavia

Aula Magna "C. Golgi"
& WEBINAR

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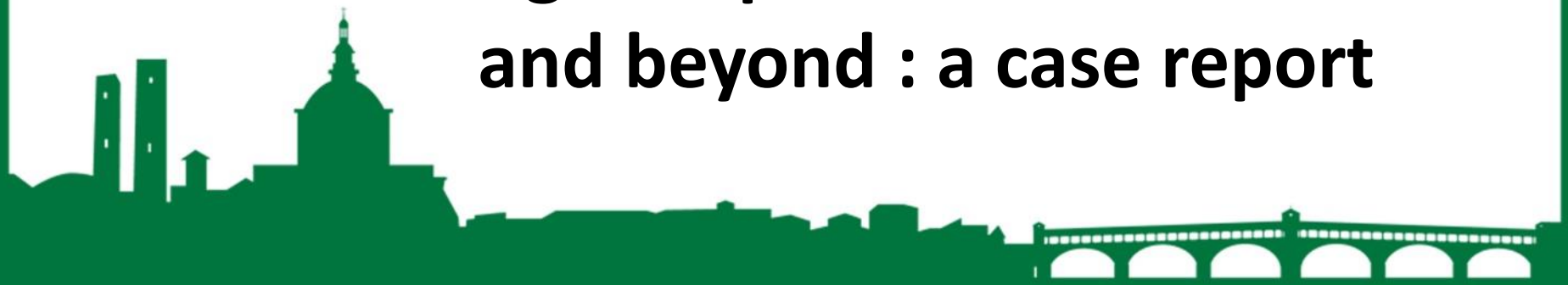
UO Pneumologia

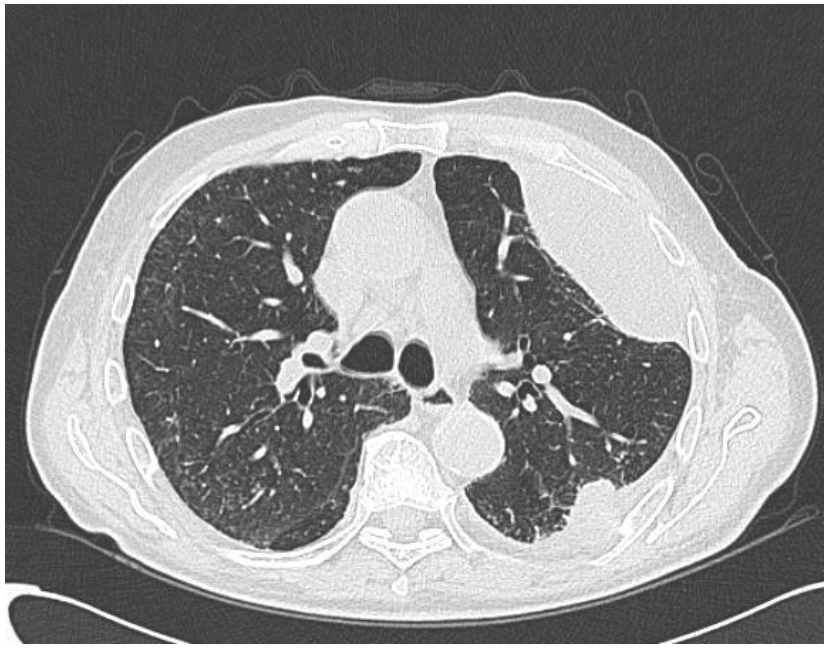
Malignant pleural mesothelioma and beyond : a case report

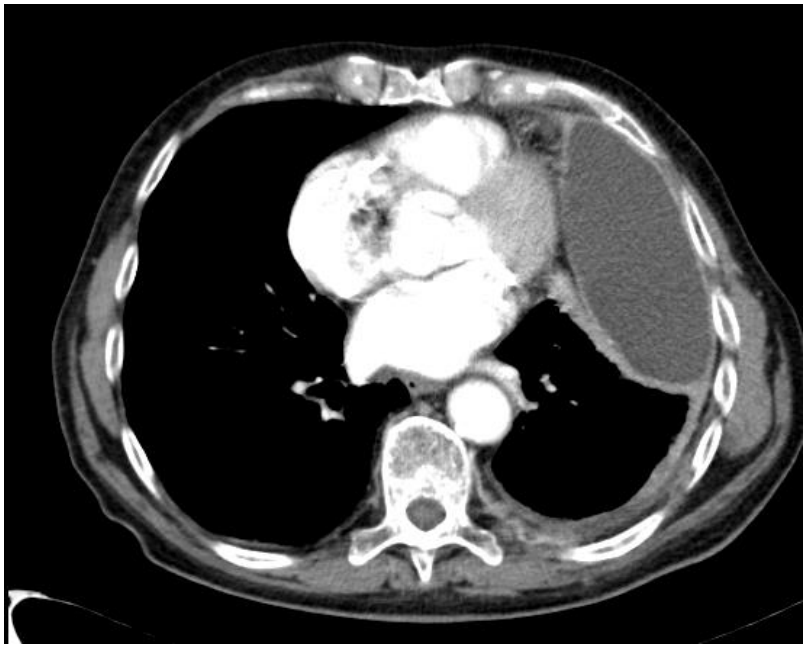


CASE REPORT

Gender	Male
Age at diagnosis	74 (2019)
Smoking history	Past smoker
Comorbidities	2007: acute myocardial infarction
Current herapy	ASA
Residence/home	Broni
Work exposure to pneumo-toxic agents	Only environmental exposure to asbestos fibers

CASE REPORT





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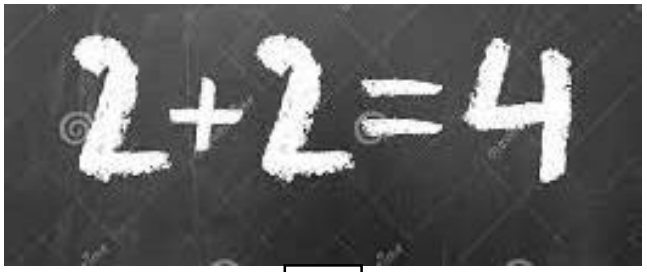
CASE REPORT

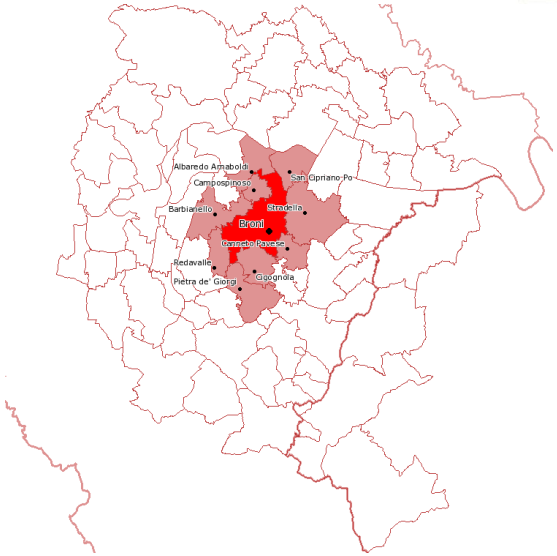


- **Pleural cancer +**
- **Environmental exposure to asbestos**

=

Malignant pleural mesothelioma

The Pavia province



Concentration of risk in Oltrepò, with town of Broni and surrounding municipalities

Fibronit plant from 1933 to 1993

3.798 workers

Asbestos is a naturally occurring fibrous material consisting of very long chains of silicon and oxygen polysilicate or long chain silicate

		Chrysotile	Crocidolite	Amosite	Anthophyllite
		%	%	%	%
Silica	SiO_2	40.3	51.4	49.3	57.2
Alumina	Al_2O_3	0.7			
Ferrous oxide	FeO	1.0	20.3	40.9	10.1
Ferric oxide	Fe_2O_3	1.5	17.5	0.4	0.1
Manganous oxide	MnO		0.1	0.7	
Calcium oxide	CaO	0.2	0.8	0.4	1.0
Magnesium oxide	MgO	42.4	1.4	5.7	29.2
Sodium oxide	Na_2O		6.2	0.2	0.1
Potassium oxide	K_2O			0.3	0.1
Carbon dioxide	CO_2	0.2	0.4	0.2	
Water of crystallization	H_2O	13.7	1.9	1.9	2.2
		100.0	100.0	100.0	100.0

		Chrysotile white asbestos	Crocidolite blue asbestos	Amosite
Approximate diameter of smallest fibers	micron	0.01	0.08	0.1
Specific gravity		2.55	3.37	3.45
Average tensile strength	lb./inch^2	350,000	500,000	175,000
Modulus of elasticity	lb./inch^2	23.5×10^6	27.0×10^6	23.5×10^6

The dose-response relationship has no established threshold and exposures at home or in the neighbourhood of sources of asbestos environmental contamination entail a substantial risk of mesothelioma

Asbestos fibers structure

Asbestos is perfectly safe in its primary state basically a type of solid rock, but is a significant health hazard when mined or worked in such a way as to produce the carcinogenic nanometer-scale fibrous particles that become airborne aerosol and are, therefore, readily absorbed in the lungs

Asbestos fibers are 2D nanoparticles = nanofibers

Biopersistence of an inhaled fiber

It is the ability of fibers to persist in the body following inhalation determines the retained dose (RD)

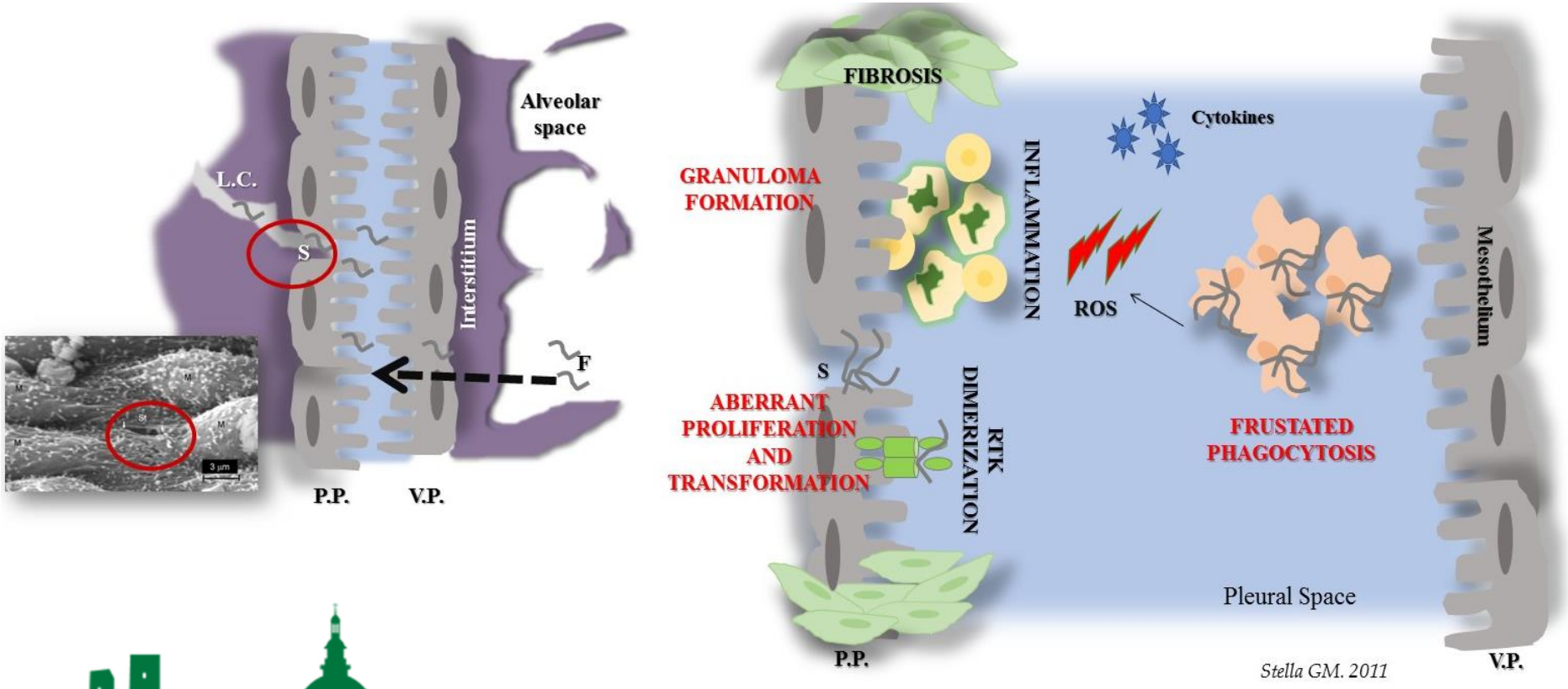
RD = total fibers deposited – cleared fibers

Mechanisms of clerance

- ✓ **Clearance via the mucociliary escalator** in the nose and tracheobronchial region
- ✓ **Phagocytosis by alveolar macrophages**
- ✓ As macrophages range in diameter from ~10 to 20 μm, shorter fibers are more likely to be completely phagocytosed by alveolar macrophages than longer fibers. This leads to incomplete or 'frustrated' phagocytosis, which is characterized by prolonged production of reactive oxygen species (ROS)
- ✓ **Dissolution** (according to pH of phagolysosome)
- ✓ **Translocation**

Chrysotile fibers may split into thinner fibrils over time.
Compared to amphiboles, chrysotile asbestos is more effectively cleared.

Pathological and biological effects induced by biopersistent fibers in the pleural space



Diagnosis → **MALIGNANT PLEURAL MESOTHELIOMA**

- Minimal biology tests and cardiorespiratory evaluation
- Basic staging for all pts fit for treatment
- Chest/abdomen CT-scan (with iodine contrast)

Patient suitable for multimodal treatment including surgery with MCR?

YES → Further staging and patient allocation → **Multimodal treatment including MCR (in expert centers only within RCT if possible)**

NO → Patient suitable for medical treatment?

YES → **Standard 1° line chemotherapy (platinum-pemetrexed+/-bevacizumab) + BSC or RCT**

NO → **BSC only including palliative RT if necessary**

RCT: randomized controlled trial
MCR: macroscopic complete resection
BSC: best supportive care

European Reference Network

Respiratory Diseases (ERN-LUNG)

- *"Mesothelioma is a malignant disease **mostly caused by asbestos**. It is most frequently located in the thoracic or abdominal cavity. Although in most countries there is legislation on the use of asbestos for many years the number of patients diagnosed with mesothelioma is still rising.*

- *This can be ascribed to the fact that **asbestos is still widely present in the western world, for instance on roofs of houses, so still people get exposed to asbestos**. Also the fact that people get older increases the risk of getting an asbestos related disease.*

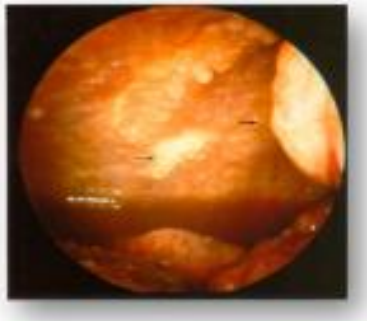
- ***Unfortunately there are no curative treatment options at this moment.***

- *Overal treatment options are limited. **The only registered treatment at present is chemotherapy**. This chemotherapy increases in general survival but the increase in time is unfortunately very limited. Surgery in mesothelioma may be an option in a limited number of patients.*

- *Fortunately there are **improvements in the knowledge** on how the disease develops, and **improvements in treatment options**. The members of the ERN mesothelioma do **together** work on these developments and provide new treatment to the patients."*

Strong association with asbestos exposure (80% of cases)

Long (20-40 yrs) of latency in individuals with a chronic exposure to asbestos



3 main different MPM subtypes

GENETIC PREDISPOSITION *(e.g. loss of BAP1)*

HISTOLOGIC, GENETIC AND MICROENVIRONMENTAL **HETEROGENEITY** AS DISEASE DRIVING FORCE

CHEMO and RT-RESISTANCE

- ASBESTOS-INDUCED TISSUE DAMAGE AND INFLAMMATION
- HYPOXIA-INDUCED STEMNESS

IMMUNOSUPPRESSIVE MICROENVIRONMENT

- HGBM1
- TAM2
- Complex T cells infiltrates

POOR RESPONSE TO CHECKPOINT INHINITORS

POOR AND SPARSE MUTATIONAL LANDSCAPE IN ABSENCE OF ONCOGENIC ADDICTION PHENOMENA

FAILURE OF TARGETED THERAPIES

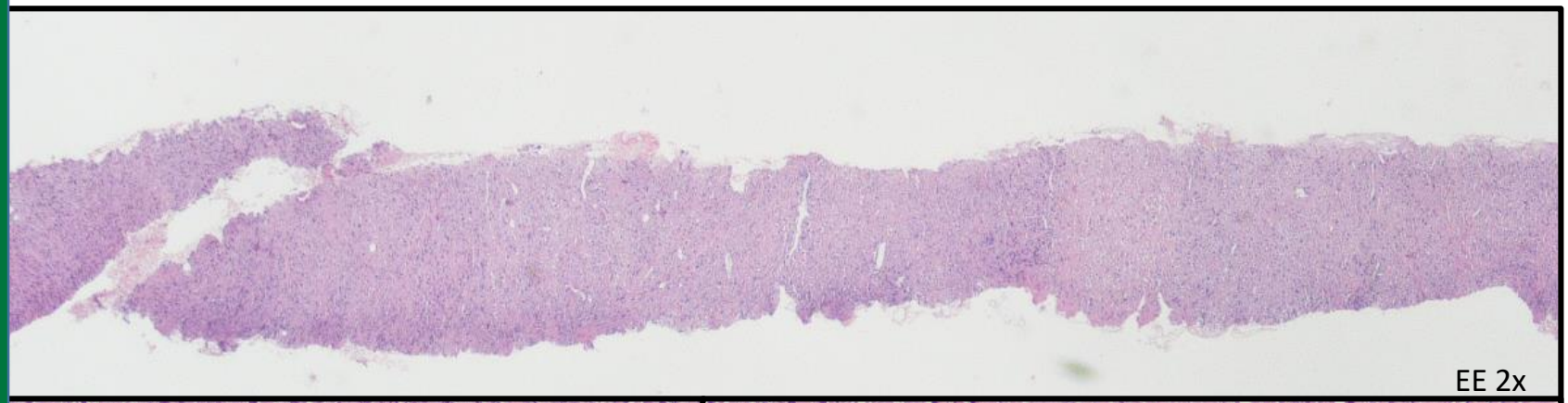
Abbott DM et al. Cancers

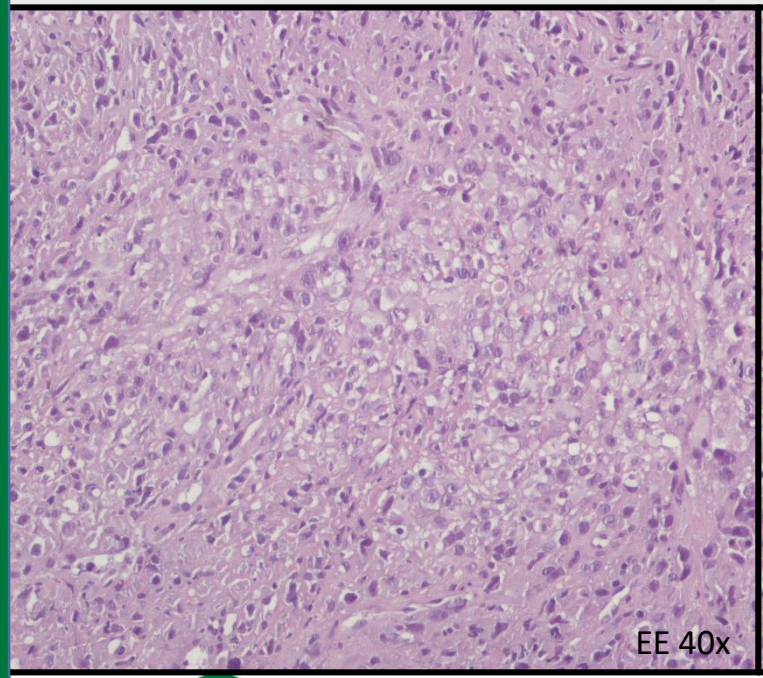
All that glisters is not…
mesothelioma

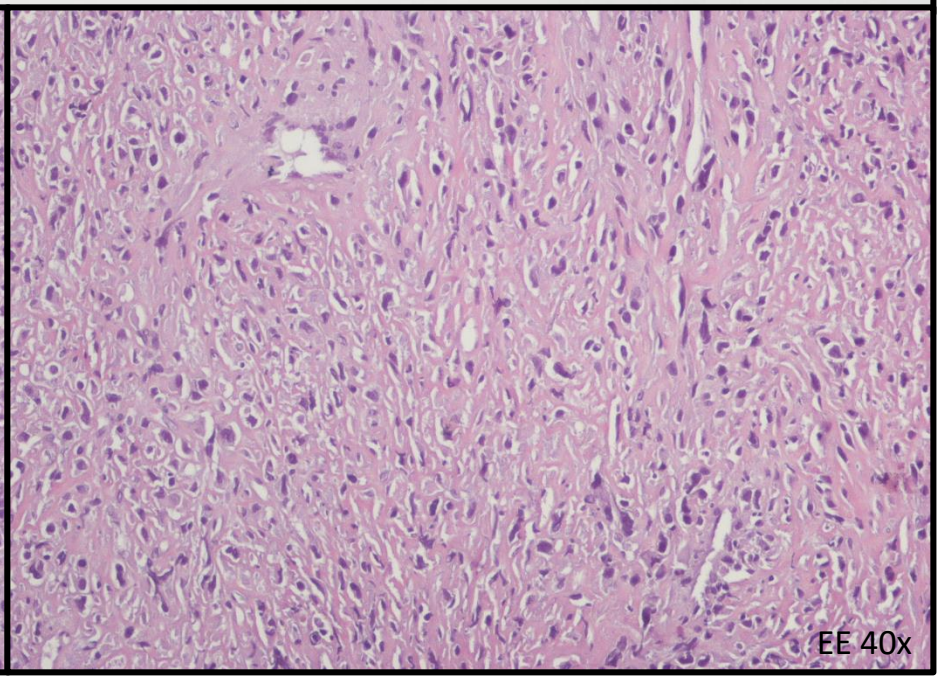
CASE REPORT

Esame istologico su biopsia pleurica = *campione agobioptico sede di diffusa infiltrazione di neoplasia scarsamente differenziata, immunoreattiva per vimentina 8, e negativa per TTF1, p40, calretinina, WT-1, D240, citocheratina 5/6, vimentina, S100, BER-EP4, CEA, CD31, CD34, desmina, miogenina*

CASE REPORT







Courtesy Prof. P.Morbini & Prof. Paulli

CASE REPORT

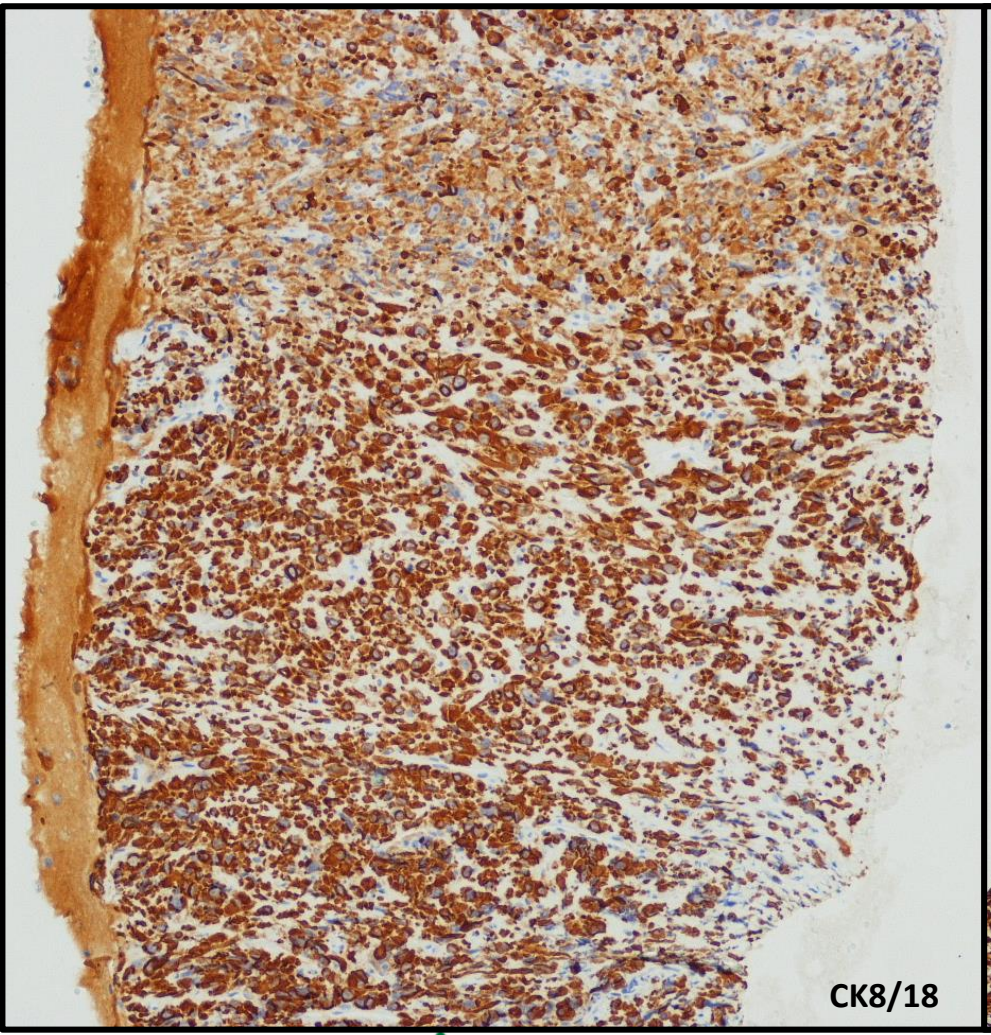
Differential diagnosis

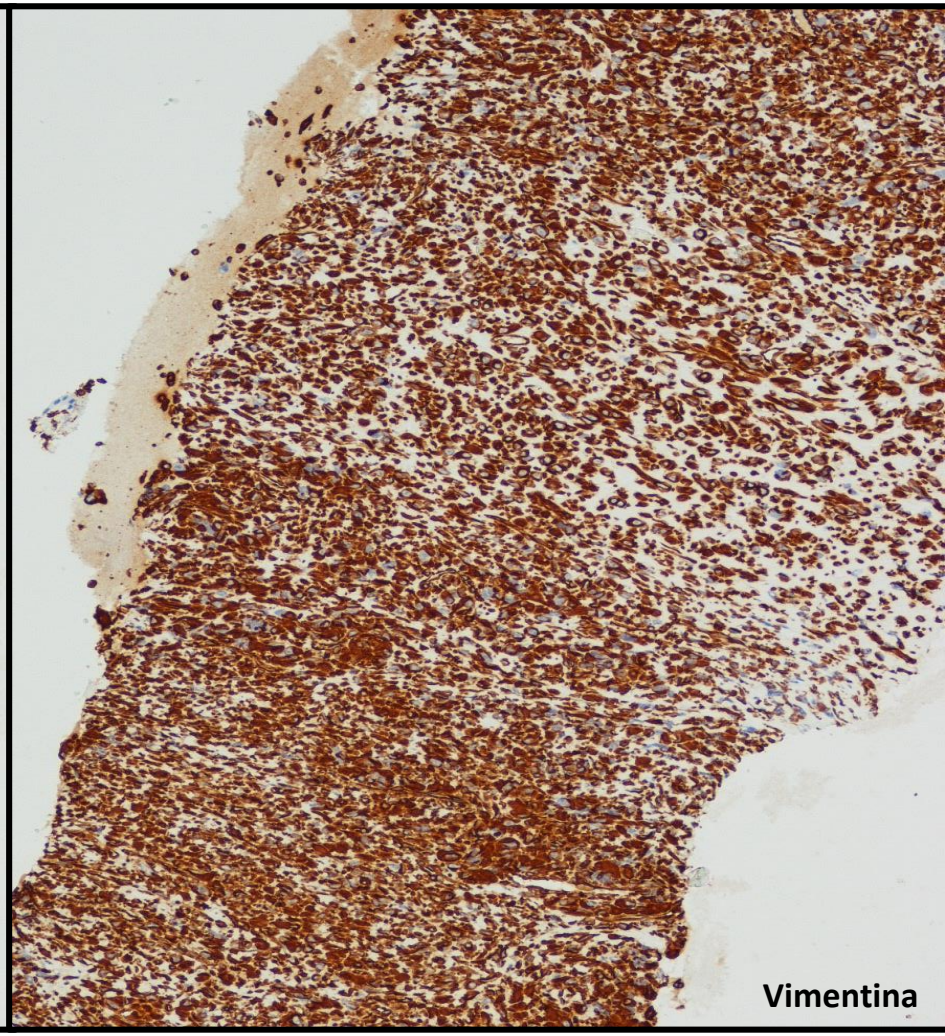
1) Undifferentiated MPM
2) Small/dormant lung primary carcinoma?
3) Melanoma?
4) Sarcoma?
5) Ectopic lung epithelial cells which undergo malignant transformation
6) Pleural localization of epithelial cancer from unknown primary site of origin

Tracking the primary

Immunohistochemistry : *ad excludendum* work-up

- S-100 negativo → ~~Melanoma~~
- CD31 e CD34 negativi → ~~Angiosarcoma~~
- Desmina e MyoD1 negativi → ~~Rabdomiosarcoma~~





Courtesy Prof. P.Morbini & Prof. Paulli

CASE REPORT

Tracking the primary : IHC staining

- TTF1 negative
- p40 negative
- CEA negative
- BER-EP4 negative

- Calretinine negative
- CK5/6 negative
- D240 negative
- WT-1 negative

Undifferentiated cancer
It is not possible a differential diagnosis between MPM and carcinoma

1. **Where is the primary?**
2. **Is there one ?**
3. **Does it really matters?**

	MPM	Indifferentiated Carcinoma
OS (M)	**15.6**	**< 6**
Therapy	Multimodal	Undefined Based on TMN stage
Actionable targets	None	No unique target validated
Growth pattern	Local	Unpredictable distant sprading

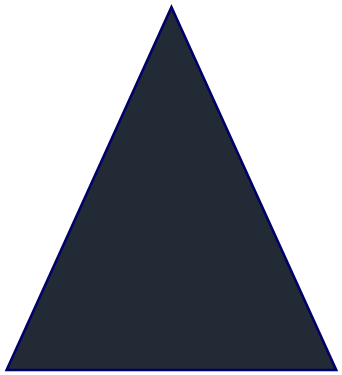
Single biological entity

Unique biological and molecular basis

Missing the primary: unrelated group of site-specific tumors which happen to share the property of having a diminutive primary which escapes diagnosis

No unique target in sigh

No validated data that unique targets work in all cancers



- Certain IHC profiles
- Latent primaries
- Responses to therapies that work for known cancers
- Which role for sampling technique and dimension?

CASE REPORT

Diagnosis	Pleural localization of indifferentiated cancer
Actionable targets	None
Therapy	Supportive care
Survival from diagnosis	5.7 months

Thanks to…

Fondazione IRCCS Policlinico San Matteo

Sistema Socio Sanitario
Regione Lombardia

Gruppo **I**nterdisciplinare
Neoplasie del **T**orace (GINT)

and to all of you for attention.