Case 3.

7-11.09.2019, 31st ECP, Nice

Małgorzata Szolkowska
National Tuberculosis and Lung Diseases Research Institute
Warsaw, Poland
• No conflicts of interest to declare
Clinical history

- 30-year old woman,
- Non-smoker,
- A mother of two children, a few days before admission she finished breast-feeding her second child;
- The patient reported long-standing contact with eternit (asbestos);
Clinical history

• CT: Mediastinal tumor infiltrating the lung, right sided hydrothorax and suspected lesions in parietal pleura, pericardium and liver

• Before admission the patient suffered from a numbness of a right half of lower lip for last two months, general weakness, periodic bone pain, headaches and vertigo
Clinical history

- **At admission**
  - in poor condition with a risk of cardiopulmonary failure

- **Physical examination:**
  - muted respiratory murmurs on the right side of the chest
  - slightly accelerated heart rate;

- Peripheral lymph nodes were not enlarged
Diagnostics

- Pleural exudate was evacuated (3500 mL) immediately after admission and a sample was sent for microscopic analysis.

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• Next day mediastinal tumor was biopsied (EBUS/TBNA).

cell block
HE

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let’s go further…
Diagnostics

• One week later a videothoracoscopic **surgical intervention** due to the multiple pleural liquid chambers and persistent right lung collapse was performed. During the procedure samples of parietal pleura, pericardium and right lung were obtained.

• **Macroscopically** pleural and pericardial samples were grey and soft, lung tissue was hyperaemic and firm without evident focal lesions.

• **Microscopically** …
Diagnostics

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Final diagnosis

NUT carcinoma

NUT midline carcinoma;

\textit{t}(15;19) carcinoma
The patient died a few weeks after establishing the final histopathological diagnosis.
NUT carcinomas - Clinical presentation

- rare,
- highly aggressive and lethal
- patients of all ages, but usually children and young adults
- no sex predilection
- mostly in midline structures, most commonly within the thorax and head and neck (the sinonasal tract)
- poor clinical outcome - death within one year
- no association with asbestos found
NUT carcinomas - Pathology

- **Histology:**
  - nests and sheets of monomorphic and **PRIMITIVE CELLS**
  - nuclei hyperchromatic or pale, irregular border, neuroendocrine-like appearance with cell-to-cell molding;
  - nucleoli are single and prominent;
  - **ABRUPT FOCI OF SQUAMOUS DIFFERENTIATION WITH KERATINISATION**;
  - brisk mitotic activity and focal or confluent areas of tumor necrosis

NUT carcinomas - Pathology

**Cytology:**

- cells dispersed singly or in small, loosely formed groups;
- numerous karyorrhectic cells and lymphocytes;
- naked nuclei

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Cytopathologic Features of NUT Midline Carcinoma: A Series of 26 Specimens From 13 Patients

Justin A. Bishop, MD; Christopher A. French, MD, PhD; and Syed Z. Ali, MD
NUT carcinomas - Immunohistochemistry

- **NUT** (nuclear protein in testis)
- usually positive: pancytokeratins, p63/p40, CD34;
- sometimes positive: EMA and BerEp4
- focal reactivity with chromogranin, synaptophysin and TTF-1;
- some described NCs were positive for CD99 or for GFAP

NUT carcinosmas - molecular findings

• fusion of *NUTM1* gene (15) with *BRD4* gene (19).

• a chimeric gene encodes the **BRD-NUT fusion protein** that inhibits differentiation and enables proliferation of neoplastic cells.

• fusion of *NUTM1* with *BRD3* or *NSD3* gene => **NUT-VARIANT CARCINOMAS**.

• A type of *NUTM1* fusion partner in NCs does not influence immunoexpression of NUT protein and patient outcome.


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NSD3-NUT Fusion Oncoprotein in NUT Midline Carcinoma: Implications for a Novel Oncogenic Mechanism

Christopher A. French1, Shaila Rahman2, Erica M. Walsh1, Simone Kühnle2, Adal R. Grayson1, Madeleine E. Lemieux2, Noam Gro watching at 3pm, Brian P. Rubin3, Cristina R. Antonescu2, Songlin Zhang2, Rajkumar Venkatramani3, Paola Dal Cin1, and Peter M. Howley2

1Department of Pathology and Laboratory Medicine, University of California, San Francisco, 2Department of Pathology, New York University, 3Department of Medicine, University of California, San Francisco
Differential diagnosis

- **morphology** => small round blue cell tumors:
  - poorly differentiated squamous cell or neuroendocrine carcinoma
  - small cell carcinoma
  - lymphoma
  - melanoma
  - SMARCA4-deficient thoracic sarcoma
  - Ewing Family of Tumors (especially a very rare subtype - ADAMANTINOMA-LIKE EWING SARCOMA)

**SMARCA4-deficient thoracic sarcoma: a distinctive clinicopathological entity with undifferentiated rhabdoid morphology and aggressive behavior**

Jennifer L Sauter¹⁴, Rondell P Graham¹, Brandon T Larsen², Sarah M Jenkins³, Anja C Roden² and Jennifer M Boland¹

**IHC**

- **loss of BRG1 (SMARCA4)**
  - cytokeratin: rare tumor cells in 10/12 cases
  - weak TTF-1 (+): 1/12 case
  - CD34 (+): 3/5 cases
  - SOX2 (+): 4/4 cases
  - negative for desmin, NUT, and S-100
Differential diagnosis

- morphology => small round blue cell tumors:
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IHC reaction with NUT antibody is crucial
Differential diagnosis

• **IHC**: weak and focal NUT (+): seminomas/dysgerminomas and embryonal carcinomas \(\Rightarrow\) germ cell tumors markers

• **genetics**: \(\textit{NUTM1}\) gene rearrangement + \(\textit{MGA}\) and \(\textit{MXD4}\): in some sarcomas

Treatment

• no efficient treatment for NC

• Recent studies suggest that inhibitors of BRD4-NUT protein (small-molecule inhibitors of bromodomain and extraterminal proteins (BET)) may induce differentiation and restrain proliferation of NC cells.

Thank you for your attention