CASE 2

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Conflict of interest/Funding

None
CLINICAL HISTORY

- 37 year-old woman; Mozambique
- Iron deficiency anemia
- Familiar history of breast cancer (grandmother)
- History of breastfeeding 2 years ago (1 child)
- Consultation for 3 months of history of a right palpable breast mass
**Physical Exam**

- Palpation of irregular nodules in supero-external quadrant of the right breast
- No skin retraction
- Enlarged right axillary lymph nodes
FINE-NEEDLE ASPIRATION

- Enlarged right axillary lymph nodes
  - No evidence of malignancy; reactive lymph node
DIAGNOSIS

- Maputo Central Hospital (Mozambique):
  - Consistent with tuberculous mastitis

- Paraffin blocks were sent to Hospital Clínica of Barcelona for special stains and PCR for *M. tuberculosis*

* tuberculous
• Ziehl-Neelsen
• Gram
• PAS
MICROBIOLOGY

- PCR amplification from paraffin-embedded tissue
- Real-time PCR for *M. tuberculosis*:
  - negative (repeated three times)
- Real-time PCR for Toxoplasma, Cryptococcus and ITS
  - negative
- 16S rRNA sequencing (weak band in agarose gel)
  - Sanger sequence of poor quality
  - No good similarities in database (Ncbi 16S rRNA BLAST)
**Diagnosis**

- Granulomatous mastitis (GM) with multinucleated giant cells and caseous necrosis..with no infectious agent identified...
- **Can we exclude TB because of negative special stains and negative TB-PCR?**
  - Exposure of paraffin block to high temperature (recent fire in pathology archive)..
  - PCR in Paraffin-embedded tissue
  - No culture done
  - No IHC done (sensitivity 64-100%)
  - Unknown serology and lack of other clinical info
- **Can we classify the case as Idiopathic Granulomatous mastitisitits (IGM)?**
The patient received 6 months standard anti-TB treatment and her symptoms resolved.
Granulomatous mastitis (GM)

- A rare entity that often mimicks malignancy
- First described by Kessler and Wolloch 1972
- Women of childbearing age
- Progressively enlarging breast lumps
  - Variable sizes
  - Firm, tender and unilateral
  - Fixed to the skin or to underlying pectoral muscle
- More frequent in African and Asian women

**Granulomatous Mastitis**

- **Imaging:** ill-defined mass
  - difficult to differentiate between carcinoma and other granulomatous diseases

- **Mammography/USE:** often “suspicious”
  - asymmetric, diffuse, increased density, hypoechoic mass lesions or nodular structures

Granulomatous mastitis (GM)

- Benign condition
- Crucial to arrive at a correct diagnosis at an early age to avoid unnecessary surgery
- Biopsy is often necessary (Gold Standard)
  - clinical and radiological findings are non-specific
  - core needle biopsy (diagnostic in 94.5% patients)
- FNA (minimally invasive, simple, cost-effective)
  - diagnostic in only 39%

**Granulomatous Mastitis (GM)**

Infectious
- *M. tuberculosis*
- *Corynebacterium*
- Fungi
- Parasites

Non-Infectious
- Sarcoidosis
- Wegener’s granulomatosis
- Foreign body reaction
- Duct ectasia

Specific GM

Diagnosis of exclusion

Excluded

Confusion in publications

Idiopathic granulomatous mastitis (IGM) (non-specific GM or Granulomatous Lobular Mastitis)
**Histology Granulomatous Mastitis**

- Irrespective of infectious, non-infectious or idiopathic..
  - Epithelioid histiocytes
  - Plasma cells
  - Lymphocytes
  - Eosinophils
  - Neutrophils
  - Multinucleated giant cells (Langhans, Touton, etc)
  - Necrosis (highly infrequent in sarcoidosis)

- Any component of breast tissue can be involved (lobules, ducts, fat)

- Rarely, carcinoma can be obscured by the granulomatous reaction (Pan-CK stains)

HISTOLOGY GRANULOMATOUS MASTITIS

- Lacambra et al, 2011:
  - Idiopathic GM may show more plasma cells compared to TB form
  - TB form shows more necrosis and eosinophils
- Idiopathic GM usually has no necrosis at all or non-caseating necrosis; more lobulo-centric
- TB mastitis involves more ducts than lobules
- Sarcoid GM shows no necrosis; less inflammation and less abscess formation

DISTINCTIVE PATTERN

- 2011: Corynebacterium (gram-positive bacilli)
- Other Gram+ bacilli/Gram+ coccus (Staphylococcus)

Cystic neutrophilic GM

- Suppurative lipogranuloma composed of a central lipid space surrounded by neutrophils surrounded by epithelioid histiocytes


Renshaw AA et al.
Cystic Neutrophilic GM

- Corynebacterium and Gram+ bacilli or coccus (Staphylococcus)

Cystic Neutrophilic GM

- The bacteria are often easy to miss on Gram stain.
- In the three cases of the first report (2011) the pathologists reported them as negative for bacteria
- Gram-positive bacteria are difficult to culture ("fastidious" bacteria)

TUBERCULOUS MASTITIS (TM)

- Uncommon even in endemic countries
- HIV-positive patients
- Majority secondary TB
- Younger patients as an abscess; in older women: simulates carcinoma
- Direct inoculation of the bacilli through abrasions (rare)
- Via lymphatic, hematogenous, or contiguous
- The lymphatic route is the most likely route: retrograde extension from the thorax to axillary lymph nodes
- Multifaceted clinical presentations: “Great masquerader”

TUBERCULOUS MASTITIS (TM)

- Different forms of presentation:
  - Nodular (slowly growing, solitary mass)

- Some authors:
  - Demonstration of caseous granulomas from the breast tissue and involved lymph nodes may be sufficient for the diagnosis..


Can we exclude TB because of negative special stains and negative TB-PCR?

- Ziehl-Neelsen
  - Overall sensitivity low (0-44%)
  - Reported positivity rates in breast tissue (TB): 12%

- TB-PCR
  - Sensitivity in fresh tissue >90%
  - Sensitivity variable (50-100%) in paraffin-embedded tissue

Can we exclude TB because of negative special stains and negative TB-PCR?

TB-PCR:
➢ Performance not extensively studied in breast tissue
➢ Positive in granulomatous breast tissue in 13% of cases compared to 65% in lymph node or lung (56.4%)

IDIOPATHIC GRANULOMATOUS MASTITIS

- Prevalence is unknown; very rare; poorly understood
- Initial insult to the ductal epithelial cells causes a transition of luminal secretions to the lobular breast stroma.
- Hyperprolactinemia or an auto-immune response to local lobular secretions play a role in pathogenesis (history of breastfeeding)
  - No specific antibodies have been identified
- Excision, steroids, methotrexate
  - No randomized, placebo-controlled trials of treatment efficacy
IDIOPATHIC GM VS CYSTIC NEUTROPHILIC MASTITIS

Overlapping histological features

However.. No Lipid Vacuoles in the Idiopathic GM

GRANULOMATOUS MASTITIS: MANAGEMENT

- Depends on the cause
- Idiopathic: steroid therapy
- Tuberculous mastitis/other infectious mastitis: steroids can exacerbate the course
- Exclude all the infectious causes before steroid therapy

TAKE-HOME MESSAGES

- More studies/series of cases should be available on GM: more clarity is needed especially for IGM
- Different types of GM can have overlapping clinical, imaging and histological features
- Some cases with TB-like histology and no infectious agent/other causes will be difficult to classify (IGM requires not to have caseous necrosis)
- Idiopathic GM is diagnosis of exclusion:
  - special stains/cultures should be negative
  - no caseous necrosis should be seen
- In cases of GM with cystic neutrophilic pattern:
  - gram stain (rule out gram-positive bacilli inside lipid vacuoles)
Thank you for your attention!!!!!