**IgG4–Related Sclerosing Mastitis (IgG4–RSM) of the Breast: An Uncommon Entity and Diagnostic Challenge on Core Biopsy**

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**Learning Objectives**

- To familiarize audience with current diagnostic criteria for IgG4–related disease (RD) in multiple organs
- Suggested terminology in breast  
  - IgG4–related sclerosing mastitis (RSM)
- To illustrate example of IgG4–RSM in breast


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**IgG4–RD**

- A spectrum of diseases recognized in multiple organs previously known under different names, such as Mikulicz syndrome, Küttner tumor (chronic sclerosing sialadenitis), Riedel thyroiditis, Ormond disease (retroperitoneal fibrosis)
- Eponyms embedded in the medical literature now known to be IgG4–related diseases (RD)
IgG4–RD

- Tumefactive lesions
- Fibroinflammatory condition:
  - 1. Lymphoplasmacytic infiltrate (IgG4–rich plasma cells)
  - 2. Storiform fibrosis
  - 3. Obliterative vasculitis
- Often, but not always, elevated serum IgG4 levels
  (IgG4 > 1.35 g/L (Normal value: 0.35–0.5 g/L))
- Frequently associated autoantibodies and decreased complement levels

Suggested Immunophenotypic Criteria for IgG4–RD Diagnosis

- Large numbers of IgG4 positive cells
  (> 50 IgG4 positive cells/HPF)
- Ratio of IgG4 positive cells to total IgG positive cells > 40%

Chronic Mastitis in Breast

- Broad spectrum of chronic inflammatory lesions in the breast of different etiology
- Abscess, diabetic mastopathy and granulomatous mastitis may present as palpable mass but these are not considered as a part of spectrum of IgG4–RD
- Breast involvement by IgG4–RSM is very uncommon and diagnostic criteria are not well defined
Material and Methods

- Retrospective pathologic work-up for possible involvement by IgG4-RSM in six patients with mass forming chronic inflammatory processes of the breast diagnosed by CB with initial diagnosis of chronic mastitis
- Six female patients (age, 23 to 73 years) presented with a single or multiple palpable breast masses
- On imaging (mammogram and ultrasound), all patients had features suspicious for malignancy
- On MRI, two patients showed enhancing high-density spiculated masses highly suspicious for malignancy

Immunohistochemistry

- IgG (DAKO, 1:40,000) and IgG4 (Light Technologies, Ltd., 1:150)
- IgG4 positivity (>50 cells/HPF) and increased ratio of IgG4+/IgG+ cells (>40%) were considered suggestive of IgG4-RD

Clinicopathologic Findings in 6 Patients with Mass–Forming Mastitis

<table>
<thead>
<tr>
<th>Age (yr.)</th>
<th>Type ofPresentation</th>
<th>Ultrasound Imaging</th>
<th>MRI</th>
<th>CB</th>
<th>HD</th>
<th>LD</th>
<th>PD</th>
<th>CBD</th>
<th>Histology</th>
<th>Staining</th>
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<tbody>
<tr>
<td>23</td>
<td>Non-palpable mass</td>
<td>6 x 8 mm</td>
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**Clinicopathologic Findings in 6 Patients with Mass–Forming Mastitis**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Type of Lesion</th>
<th>Histological Features</th>
<th>Immunohistochemical Markers</th>
<th>Table: Antibodies</th>
<th>Serum IgG4 Levels</th>
<th>Excisional Biopsy</th>
<th>Excisional Biopsy Result</th>
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<tbody>
<tr>
<td>RNS</td>
<td>N/A</td>
<td>Dense lymphoplasmacytic infiltrate</td>
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**Work –up for IgG4–RD in the Breast**

- In one case, the initial diagnosis of inflammatory pseudotumor was suggested
- Multinucleated giant cells and rare non-caseating granulomata in 3 cases
- Two patients with diffuse lymphohistiocytic infiltrate and axillary lymphadenopathy: lymphoma work–up negative
- Serum IgG4 levels tested in 2 cases: normal limits

**All Cases**

- Dense lymphoplasmacytic infiltrate
- Stromal sclerosis
- Loss of acinar architecture
- Negative stains for acid–fast bacilli and GMS
- No obliterative phlebitis
- No excisions performed in any cases
Histopathologic study is essential to determine non-malignant nature of chronic inflammatory infiltrate and to rule out infectious etiology.

Patient subjected to multiple biopsies in breast and lymph nodes to rule out epithelial malignancy and for lymphoma work up.

Epithelial malignancy, infectious etiology, and other systemic sclerosing diseases must be ruled out.

Clinical Presentation of IgG4-RSM
Summary

- A constellation of morphology, increased IgG4+ plasma cells and IgG4/IgG ratio in an appropriate clinical context is required for diagnosis of IgG4-RD in the breast
- A caution is needed not to over interpret a focal IgG4 positivity in small CB samples which may be merely nonspecific
- At this point more cases are needed to suggest steroid/immunomodulatory therapy for IgG4–RSM with system organ involvement

Questions

1. It is unclear if same diagnostic criteria can be applied to limited CB samples that have become standard for diagnosis of breast lesions
2. Does diagnosis of IgG4–RSM should be considered if a breast is a single organ involved by the disease?