**Zebras in Dermatopathology**

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**Disclosure of Relevant Financial Relationships**

Dr. Gonzalo de Toro declares he has no conflict(s) of interest to disclose.

**CASE 1**

Zebras in Dermatopathology. Relatively rare entities that may be missed in a skin biopsy with serious consequences

**Clinical History**

- A 30-year-old woman presented to the Puerto Montt Hospital in August 2012 by progressive dyspnea on exertion. Also, she was seeking cosmetic treatment of multiple facial papules that had been gradually increasing in number over the past three years.

**Clinical History**

- She had a medical history of epilepsy, hypothyroidism and a surgical procedure in 2009, for a skin colored firm, plaque over her forehead. A descriptive diagnosis was made, referring fibrosis, sebaceous hyperplasia and follicular dilatation.
- At that time, she was diagnosed as having facial acne vulgaris and was prescribed topical antibiotics. However, no improvement was noticed.
• http://clinicalgate.com/

Case 1

Clinical History:
A 26-year-old woman presented to the Puerto Montt Hospital in August 2012 for progressive discomfort on the right side of her face. At that time, she was undergoing systemic treatment for a skin lesion that had been gradually increasing in number over the past three years. She had a medical history of epidermolysis bullosa, affecting the skin and mucous membranes, leading to frequent skin infections and scar formation. A review of her medical records revealed that she had been treated with topical antibiotics and systemic medication, but her symptoms persisted. A biopsy of the lesion was performed, revealing histological findings consistent with epidermolysis bullosa.
Zebras in Dermatopathology

Differential Diagnosis

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Folliculocystic and collagen hamartoma of tuberous sclerosis complex

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Abstract: A 46-year-old man presented with a 1-year history of multiple dermal nodules of the chest and upper abdomen. Most of these nodules were firm and slightly tender to palpation. Biopsy of one of the lesions showed a folliculocystic hamartoma with a combination of follicular hamartomas and collagen hamartomas. The histological features of this lesion were similar to those described in tuberous sclerosis complex (TSC) and the diagnosis was confirmed by immunohistochemistry and ultrastructural examination. The findings suggest that the folliculocystic hamartoma is a distinct entity related to TSC.

Keywords: Tuberous sclerosis complex, folliculocystic hamartoma, collagen hamartoma

Folliculocystic and collagen hamartoma of tuberous sclerosis complex

Fig. 1. Patient 1. A large area of thickened skin with multiple, firm, yellowish nodules in both buttocks and right shoulder, several years of evolution. B. A large, firm, yellowish nodule with a central keratin plug, typical of a folliculocystic lesion.

Discussion

Six children presented with complex hamartomas composed of thickened skin, hyperkeratosis, cyst formation, and areas of atrophy. These lesions were distributed on the face, upper limbs, and trunk. The histological examination of these lesions showed the presence of multiple, small, keratin-filled cysts in the dermis. The cysts were lined by a single layer of keratinocytes and contained a proteinaceous material. The underlying dermis was thickened and showed a mixed inflammatory infiltrate. The diagnosis was confirmed by immunohistochemistry, which showed the presence of tuberin and hamartin, proteins that are characteristic of TSC. The histological features of these lesions were similar to those described in TSC, but the clinical presentation was different, with a more widespread distribution of the lesions. The findings suggest that the folliculocystic hamartoma is a distinct entity related to TSC.

Fig. 2. A. Gross pathology (patient 1): a large nodule with a central keratin plug, typical of a folliculocystic lesion. B. A section of the dermis showing a mixed inflammatory infiltrate with large inflammatory cysts. C. Immunohistochemistry showing the presence of tuberin and hamartin.
What about our patient?

Table II. Clinical features of patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Location</th>
<th>Other extracutaneous features</th>
<th>Other signs</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Early Infancy</td>
<td>Abdomen</td>
<td>Hypopigmented macules, Angiobromas, Periungual fibromas</td>
<td>CNS tubers, Telangiectasia</td>
<td>Seizures, Mental retardation</td>
<td>Definite TSC, Sporadic</td>
</tr>
<tr>
<td>2</td>
<td>Infant</td>
<td>Lumbar</td>
<td>Hypopigmented macules, Angiobromas, Periungual fibromas</td>
<td>Frontal plaque, Calibrated CNS tubers</td>
<td>Seizures</td>
<td>Definite TSC, Sporadic</td>
</tr>
<tr>
<td>3</td>
<td>Infant</td>
<td>Lumbar</td>
<td>Hypopigmented macules, Angiobromas, Periungual fibromas</td>
<td>Gingival fibromas</td>
<td>None</td>
<td>Definite TSC, Sporadic</td>
</tr>
<tr>
<td>4</td>
<td>Infant</td>
<td>Occipital</td>
<td>Hypopigmented macules, Angiobromas, Periungual fibromas</td>
<td>Occipital tumor, Cardiac hypertrophy</td>
<td>None</td>
<td>Definite TSC, Sporadic</td>
</tr>
<tr>
<td>5</td>
<td>Early Infancy</td>
<td>Occipital</td>
<td>Hypopigmented macules, Angiobromas, Periungual fibromas</td>
<td>Subepidermal nodules, Calibrated CNS tubers</td>
<td>Seizures</td>
<td>Definite sporadic TSC (1995 in Table II of TSC)</td>
</tr>
<tr>
<td>6</td>
<td>Infant</td>
<td>Right thigh</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

CNS: Central nervous system, M: male, TSC: tuberous sclerosis complex.

*No clinical evidence of TSC by age 3 yrs, no brain or renal imaging studies performed to date.
FOLLICULOCYSTIC AND COLLAGEN HAMARTOMA OF TUBEROUS SCLEROSIS COMPLEX

- Folliculocystic and collagen hamartoma was suggested as a new type of complex hamartoma related with tuberous sclerosis complex (TSC) in 2012 by Torrelo et al.
- They reported six cases of complex hamartomas showing thick collagen deposition, concentric perifollicular fibrosis, and keratin-filled infundibular cysts, and that clinically appeared as a large thickened plaque studded with multiple comedo-like openings and keratin-containing cysts.

Among the six patients, five had central nervous system and/or cardiac manifestations of TSC, and had a diagnosis of TSC according to the currently accepted diagnostic criteria; therefore, it seems that the two disorders are causally related.

Histopathology

- Perifollicular fibrosis
- Comedo-like dilatations
- Abnormal hair follicles
- Collagen deposition
- Infundibular cyst formation. Infundibular cyst formation is not observed in shagreen patches of TSC and other TSC-unrelated collagen nevi; thus, these characteristic histopathologic features are recognized to form a distinctive hamartomatous skin lesion.
Tuberous sclerosis complex

- The prevalence of TSC is estimated at 1/10,000, and about two-thirds of the cases are sporadic with no family history due to new mutational events.
- TSC is due to inactivating mutations in either of two genes, TSC1 (on chromosome 9q34) or TSC2 (on chromosome 16p13.3).

- The TSC genes TSC1 and TSC2 encode proteins, termed hamartin and tuberin respectively, that form a functional complex.
- TSC1/TSC2 functions as a GTPase-Activating Protein (GAP) towards Rheb, which is a major regulator of the mammalian target of rapamycin (mTOR).
- In the absence of either TSC1 or TSC2, high levels of Rheb-GTP lead to constitutive activation of mTOR–raptor signalling, thereby leading to enhanced and deregulated protein synthesis and cell growth.

Cutaneous findings of TSC

- Facial angiofibromas,
- Periungual fibromas (Koenen’s tumor),
- Gingival fibromas,
- Shagreen patches (plaque of collagenoma),
- Fibrous plaque of the forehead,
- Folliculocystic and collagen hamartoma (still not a criteria)
- and ashleaf macules.

- In terms of abundant collagen deposition in the dermis of TSC, folliculocystic and collagen hamartoma might be considered an atypical type of shagreen patches.

Clinical History:

- A 57-year-old woman without medical history presents to the dermatology clinic with a two months history of multiple violaceous and painful subcutaneous nodules on her left leg. In the last 2 weeks, she developed a 5 cm ulcer on her left calf. A biopsy was taken from that area. Additionally, she is referring a mild rhinorrhea starting the last month.
Extranodal NK/T cell lymphoma, extranasal type

- Non-Hodgkin lymphoma presents in extranodal sites in about 40% of patients.
- Extranodal lymphoma of the paranasal sinuses is a rare clinical entity seen only in 5–8% of extranodal lymphomas of the head and neck.
- Nasal NK/T cell lymphoma (NKTCL), which is a subtype of peripheral T cell lymphoma, constitutes about 1.4% of all lymphomas.

Extranodal NKTCL nasal type is an NK cell-derived neoplasm.

- It usually affects the aerodigestive tract (e.g., nose, oropharynx, and larynx), but skin, gastrointestinal, and testis involvement can occur.
- It is a locally destructive tumor mainly affecting the midface, hence its old name "lethal midline granuloma".

Epidemiology

- NKTCL is seen more in Asian and Latin-American countries. It has a male-to-female ratio of 2:1 to 3:1 and mainly affects patients in their 60s.
- EBV also has a role in the development of this neoplasm.

Clinical Features

- In general, NKTCL presents with nonspecific symptoms.
- Weight loss, fever, night sweats, and anemia are usually only encountered in late stages.
- The nasal variety can cause nasal obstruction, epistaxis, rhinorrhea, extensive midfacial structure involvement of the orbit causing proptosis, and, occasionally, the hard palate.

- Clinically, it can be divided into nasal and extranasal types;
  - the nasal variety commonly presents with nasal obstruction, but also it can cause epistaxis, extensive involvement of the midfacial structure, involvement of the orbit causing proptosis, and, occasionally, the hard palate.
  - In extranasal variety, skin is the most common site of involvement, but it can affect the gastrointestinal system, spleen, and testes. Muscles and adrenal glands are rarely involved.

- The extranasal type usually disseminates early in the course of the disease, but most were found to have occult nasal primaries.
- Nasal panendoscopy should be done irrespective of the primary site of presentation.
Morphology

- Histologically, the neoplasm shows ulceration; angiocentric and angiodestructive growth is seen with areas of necrosis and lymphocytic infiltration with irregular nuclei on the surface of the epithelium and subepithelium, which is called polymorphic reticulosis.
- The tumor tends to cause coagulative necrosis in the tissue, so a large biopsy should be taken.

Immunohistochemistry

- The immunophenotypes of these tumors are CD2+, CD56+, and cytoplasmic CD3+. Cytotoxic molecules (Granzyme B, TIA-1, and Perforin) are positive, and often show negative expression of T cell antigen (e.g., CD4, CD5, and surface CD3) and negative for B cell marker CD20.
- DDx
  - Blastic plasmacytoid dendritic cell neoplasm (BPDCN): CD123 (+)
  - Leukemia cutis

Prognosis

- The prognosis of the disease is variable; it is generally poor, with a 30% 5-year survival rate, but it recently increased to 71% due to utilizing intensive therapy like up-front radiotherapy.
- Multiple factors affect the prognosis:
  - age of the patient,
  - stage of disease,
  - EBV DNA level,
  - number of extranodal sites,
  - LDH level, and
  - regional lymphadenopathy.
- Extranasal NKTCL in general has a worse prognosis than nasal type, as patients tend to have B symptoms (fever, night sweats, and weight loss) and involvement of the lymph nodes.

Treatment

- A combination of radiotherapy and chemotherapy is the best modality of treatment, especially for the early stages, because of the high recurrence rate when radiotherapy alone is used.
- Regimens like SMILE (Dexamethasone, Methotrexate with Leucovorin, Ifosfamide, L-asparaginase, and Etoposide) can be used; it has an 86% response rate (RR). If radio-therapy is used, the RR increases to 89.7% and the response is durable.
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