IRAP
March 2017
NorthShore University HealthSystem

Case #1:

PRESENTER: Muhammad Ahmad, MD
ATTENDING: Curtis R. Hall, MD

CASE HISTORY:
A 63-year-old male presented with nocturia, urinary urgency, frequency, hesitancy and slow urine stream. Subsequent CT scan of the abdomen and pelvis revealed moderate to marked right-sided hydronephrosis and hydroureter to the level of the right ureterovesical junction. The patient underwent laparoscopic right nephroureterectomy.

DIAGNOSIS: Proteinaceous deposition compatible with immune protein deposition disease.

DISCUSSION:
- This is a case of deposition of Congo red negative amyloid or amyloid-like material in the ureter, causing hydronephrosis. There haven't been many such cases reported in the literature.
- An amyloid fibril protein is a protein that is deposited as insoluble fibrils, mainly in the extracellular spaces of organs and tissues as a result of sequential changes in protein folding, that results in a condition known as amyloidosis.
- Occurs in tissue deposits as rigid, non-branching fibrils which usually bind the dye Congo red and exhibit green, yellow or orange birefringence when viewed under polarized light. There are reports in literature of Congo red negative cases of amyloid.
- There is no real consensus of pathologists on the meaning of "true" Congo red positivity. Some consider salmon pinkish hue on Congo red staining as positive. Others believe that it has to be salmon pink on Congo red as well as birefringent under polarized light to be called positive.
- The International Society of Amyloidosis has suggested that birefringence can be green, red, yellow or a spectrum of colors, and not necessarily only apple green.
- Amyloidosis presents in a variety of ways, in part because of the many different types of amyloid. Treatments are available for many types of amyloidosis but they are type-specific. Therefore, it is essential to diagnose the exact type of amyloid.
- Laser microdissection followed by mass spectrometry is the gold standard for definitive diagnosis for amyloid. Because LMD-MS directly analyzes the actual peptide, it can identify the protein with or without known mutations.

QUESTIONS:

1. Congo red staining can be influenced by which of the following?
   - A. Biopsy site
   - B. Staining techniques
   - C. Fixation time
   - D. All of the above

2. Which of the following types of amyloids is most frequently associated with familial amyloidosis?
   - A. AL type (primary amyloidosis)
   - B. AA type (secondary amyloidosis)
   - C. Beta 2 microglobulin type
   - D. ATTR type (transthyretin)

ANSWERS:

1. (D). All of the above

Explanation: Congo red staining can be influenced by a number of factors including biopsy site (tissue source), staining techniques, type of fixative used, fixation time, amount of protein deposited, precursor protein deposited, inadequate tissue quantity, improper use of the polarizing instrument and poor light intensity

2. (D). ATTR type (transthyretin)

Explanation: ATTR type is associated with familial amyloidosis. Amyloid fibrils consist of transthyretin. AL type also called primary amyloidosis is the most common cause of renal amyloidosis in US. AA type also called secondary amyloidosis is associated with chronic inflammatory conditions such as osteomyelitis, bronchiectasis, decubitus ulcers, Crohn's disease, rheumatoid arthritis and tuberculosis etc. Beta 2 microglobulin type is associated with long-term hemodialysis or peritoneal dialysis. Its deposits occur in blood vessel walls, perineural and periarterial tissue, bone, joint, skin, subcutaneous tissue, heart, GI and lungs. It may cause carpal tunnel syndrome, joint disease and bone cysts.

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Case #2:

PRESENTER: Indu Agarwal, MD
ATTENDING: William G. Watkin, MD

CASE HISTORY:
A 33 year old female with a history of nephrolithiasis was noted to have a 4.5 cm right renal mass on MRI. A radical nephrectomy was performed.

DIAGNOSIS: Tubulocystic renal cell carcinoma

DIFFERENTIAL DIAGNOSES:
- Multilocular cystic RCC
- Cystic nephroma/ MEST
- Collecting duct carcinoma
- Type 2 Papillary RCC
- Tubulocystic carcinoma
- Oncocytoma with prominent tubules and cysts

DISCUSSION:
- **General:**
  - An uncommon cystic renal epithelial malignancy. It constitutes <1% of all renal carcinomas. There is male predominance, age ranges from 30-94 years, mean age of 58.4 years. 60% discovered incidentally.
- **Histopathology:**
  - Small to intermediate sized tubules admixed with larger cysts, lined by a single layer of flattened, cuboidal/columnar, and hobnail epithelium. Nuclei are enlarged and irregular, with intermediate to large G3 nucleoli. Cytoplasmic features include abundant eosinophilic oncocytoma-like aspects. The stroma is fibrotic. No areas of solid growth
- **Immunohistochemistry of TCRCC:**
  - Positive stains: AMACR, CD10, CK8/18, CK7, CA-IX , PAX2/PAX8 , Parvalbumin, Kidney specific cadherin
  - Negative stains: CD117
- **Prognosis and behavior:**
  - Majority behave indolently, of the 100 reported cases only 1 recurred and only 4 cases metastasis.
- **Genetics:**
  - Gains of chromosome 7 and 17 and loss of the Y chromosome, suggesting a close relationship with papillary RCC.
  - More studies have shown gains of 17 than 7

QUESTIONS:

1. Which of the following tumor of kidney is associated with gains of chromosomes 7 and 17?
   A. Collecting duct carcinoma
   B. Chromophobe renal cell carcinoma
   C. Tubulocystic renal cell carcinoma
   D. Cystic nephroma

2. Which of the following statements is true of renal neoplasms?

A. Collecting duct carcinoma and tubulocystic carcinoma have same genetic molecular profile.
B. Poorly differentiated foci in tubulocystic carcinoma are associated with *fumarate hydratase* mutation.
C. Clear cell renal cell carcinoma generally stains positive for CK7.
D. Box like staining pattern of CA-IX is characteristic of clear cell papillary RCC.

ANSWERS:
1. (C), reference 7
2. (B), reference 6

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Case #3:

PRESENTER: Talent Theparee, MD
ATTENDING: Mohamed Eldibany, MD

CASE HISTORY: A 51-year-old female presented with self-palpated inguinal lymphadenopathy. She denied any change in weight, infections, or limb swelling. She did not have any fevers or night sweats, but noted malaise starting approximately two months previously. MRI scanning of the abdomen and pelvis demonstrated an enlarged right inguinal lymph node (5.8 cm) and additional enlarged lymph nodes in the right inguinal, iliac, and pelvic sidewall region. The patient underwent a regional inguinal lymph node biopsy.

DIAGNOSIS: Atypical paracortical CD4+CD8+ T-cell proliferation consistent with indolent T-lymphoblastic proliferation.

IMPORTANT DIFFERENTIAL DIAGNOSES:

- T-lymphoblastic lymphoma
- Ectopic thymic tissue
- Metastatic thymoma/thymic carcinoma

KEY DIAGNOSTIC FEATURES:

- Rare tumor of unknown etiology, first described in 1999
- Non-clonal proliferation of immature T-lymphocytes in lymphoid tissues
    - Sites: oropharynx, mandibular, cervical, supraclavicular, abdominal, retroperitoneal locations
- Histology:
    - Interfollicular lymphoid expansion with general preservation of lymphoid architecture
    - Lymphocytes are usually small with minimal cytoplasm and no nuclear atypia.
    - Chromatin pattern typically ranges from fine to condensed with inconspicuous nucleoli
    - Can be mitotically active with scattered histiocytes
- Immunophenotype: Immature T-cells
    - Generally positive for TdT, CD1a, CD3, CD4, CD8
    - Variable expression of CD2, CD5, CD7, CD10, CD33, CD99
    - Negative for CD34, CD20, CD79a
- Treatment and prognosis: indolent clinical course; case reports document survival over decades with only surgical debulking and no cytotoxic therapy
- Case reports have document occurrence alongside Castleman's disease, myasthenia gravis, hepatocellular carcinoma, angioimmunoblastic T-cell lymphoma, acinic cell carcinoma
    - Cause for co-occurrence theorized to be due to cytokine milieu of tumors
    - No definite relationship has been proven

QUESTIONS:

1. Which of the following features can help distinguish indolent T-lymphoblastic proliferation from acute T-lymphoblastic lymphoma?
    A. Infiltrating pattern obliterating normal lymphoid architecture with nuclear atypia
    B. Co-expression of CD4 and CD8
    C. High mitotic activity detected by Ki-67
    D. Flow cytometric detection of CD7+ lymphocytes

2. Indolent T-lymphoblastic proliferation has occurred with which of the following conditions?
    A. Sinus histiocytosis with massive lymphadenopathy
    B. Adenocarcinoma
    C. Hepatocellular carcinoma
    D. Myeloid sarcoma

ANSWERS:

1. A (REF 3).
2. ~~D~~ C (REF 5).

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Case #4:

PRESENTER: Crystal Bockoven, MD
ATTENDING: Megan Sullivan, MD; William G. Watkin, MD

CASE HISTORY: A 64-year-old female presented with postmenopausal bleeding. An endometrial biopsy was unable to be performed due to pain and a pap smear was negative. The physical exam was unremarkable. Pelvic ultrasound showed a 10.6 cm complex right adnexal mass and a CT of the pelvis revealed a 14.4 cm right adnexal mass with a 10.7 cm solid component. A CA 125 was 49.7 units/mL. Please see glass slide.

DIAGNOSIS:

Non-HPV associated endocervical adenocarcinoma, gastric type

DISCUSSION:

- **Cervical Gastric-Type Adenocarcinoma (GAS)**
  - Kojima and colleagues- defined GAS in 2007
  - The most common non-HPV related variant of cervical adenocarcinoma
  - Well-differentiated GAS ~1% of cervical adenocarcinomas
  - In its extremely well differentiated form, it was formerly called minimal deviation adenocarcinoma or adenoma malignum

- **Histology**:
  - Architecture: glands highly variable in size and shape
  - Cytology: abundant clear eosinophilic cytoplasm, distinct cell membranes, and basal nuclei
  - Haphazard growth in stroma
  - Inflammatory infiltrate

- **Staining profile**:
  - Positive: MUC6, HIK1083, p53, CK7, CEA
  - Negative: p16, ER, PR

- Lobular Endocervical Glandular Hyperplasia is a possible precursor

- **Genetics**:
  - Mutations in the LKB1 (STK11) gene, found as a germ-line mutation in Peutz-Jeghers Syndrome, has an associated with GAS

- **Diagnostic challenges**:
  - Well-differentiated form may be hard to differentiate from normal endocervical glands
  - Screening is a challenge (cytologically bland, high risk HPV will be negative)

- **Prognosis**:
  - 5 year disease-free survival of ~30% (compared to ~74% for usual HPV-related cervical adenocarcinomas)

QUESTIONS:

1. What is a possible precursor lesion for gastric type mucinous adenocarcinoma?
   A. Adenocarcinoma in situ
   B. Lobular endocervical glandular hyperplasia.
   C. Microglandular hyperplasia

2. What is a common genetic alteration associated with well-differentiated gastric type mucinous adenocarcinoma?
   A. *APC* gene
   B. *EGFR* gene
   C. *STK11* gene

ANSWERS:

1. (b), reference: 3
2. (c), reference: 1

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Case #5:

PRESENTER: Jamaal Rehman, M.D.
ATTENDING: Thomas Cibull, M.D.

CASE HISTORY: A 74-year-old Asian male presented to the outpatient clinic with recurrent well-demarcated erythematous nodular and ulcerated skin lesions on the right posterior thigh which spontaneously remit and heal over the course of several months. His past medical history is significant for similar lesions that have occurred throughout many years. Aside from the patient's presentation, a review of systems was unremarkable and demonstrated pertinent negatives, such as no fever, chills, or lymphadenopathy.

DIAGNOSIS: Lymphomatoid papulosis, type E

IMPORTANT DIFFERENTIAL DIAGNOSES: Anaplastic large cell lymphoma, Gamma-delta T-cell lymphoma, CD8+ Aggressive epidermotropic cytotoxic T-cell lymphoma, Angioimmunoblastic T-cell lymphoma, NK/T-cell lymphoma

KEY DIAGNOSTIC FEATURES:

- Clinical - Lesions wax and wane with spontaneous remission
- Gross - Well-demarcated erythematous papules, plaques, and nodules, some with ulcerations
- Histology - Dense infiltrate of atypical lymphocytes surrounding and infiltrating blood vessel walls
- Staining - Positive: CD2, CD3, CD4+/-, CD8+/-, CD30, CD56+/-, beta F1
  - Negative: CD20, ALK, EBER
- Treatment - Methotrexate, Psoralen with Ultraviolet phototherapy
- Key points - WHO CD30+ T-cell lymphoproliferative disorder
  - Lesions wax and wane with remission (vs. lymphoma)
  - No systemic symptoms or clinically aggressive course (vs. lymphoma)
  - Dense infiltrate of atypical lymphocytes (similar to lymphoma)

QUESTIONS:

1. Which of the following is true regarding Lymphomatoid papulosis?
   A. The lesions generally persist with worsening of symptoms over time
   B. The patient usually has a past medical history of similar lesions
   C. Fevers, night sweats, and lymphadenopathy are predictive of a worse outcome
   D. The majority of patients progress to lymphoma

2. What are the histologic types of Lymphomatoid papulosis?
   A. Small cell type, large blue cell type, mixed histiocytic type, and angiocentric type
   B. Lymphocytic-rich type, mixed cellularity type, classical type, nodular sclerosing type
   C. Histiocytic type, lymphocytic type, epidermotropic T-cell lymphoma type, angiocentric type, and follicular type
   C. Histiocytic type, plasma cell type, eosinophil type, and lymphocytic type

ANSWERS:
1. B (Reference 6)
2. C (References 1 and 3)

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Case #6:

PRESENTER: Sharif Nasr M.D.
ATTENDING: Thomas Cibull M.D.

CASE HISTORY: The patient is a 58 year old with a recurrent and persistent left lower eyelid lesion. She had a similar lesion in the same location previously which was partially excised.
DIAGNOSIS: Endocrine mucin producing sweat gland carcinoma (EMPSGC)

IMPORTANT DIFFERENTIAL DIAGNOSES: Apocrine hydrocystoma/cystadenoma; acrospiroma (hidradenoma); sebaceous carcinoma; basal cell carcinoma; metastatic breast carcinoma.

KEY DIAGNOSTIC FEATURES:
- Etiology of tumor:
  - Sweat gland carcinoma.
- Gross:
  - Slow growing fleshy papule or fluid filled cyst.
- Cytology:
  - Nodular aggregates of amphophilic basaloid cells with bland nuclei.
  - Stippled chromatin and inconspicuous nucleoli
- Histology:
  - Nodular aggreagates of basaloid cells in dermis, can be solid or partially cystic.
  - Intracytoplasmic or extracellular mucin can be present
- Staining profile:
  - Positive: ER/PR/CK7/Synaptophisin/chromogranin/BerEP4
  - Negative: CK20/S100
- Unfavorable predictive factors:
  - Concurrent invasive mucinous adenocarcinoma.
- Treatment:
  - Surgical excision with follow-up.

QUESTIONS:

1. EMPSGC is thought to be a precursor lesion to which of the following?
    A. Hidradenocarcinoma
    B. Basal cell carcinoma
    C. Mucinous adenocarcinoma

1. Where is EMPSGC almost always located?
    A. Lower eyelid or upper check
    B. Lower lip
    C. Can occur throughout the body

ANSWERS:
1 – C (Reference 5)
2 – B (Reference 6)

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