Reed's syndrome – a case study

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INTRODUCTION:

First reported by Finish investigators 16 years ago, Reed's Syndrome or Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) is an inherited susceptibility to uterine and cutaneous leiomyomas and renal cell carcinoma. The syndrome has been linked to a germline mutation in the **fumarate hydratase (FH) gene** that encodes a Krebs cycle enzyme which transforms fumarate to malate. This mutation, transmitted in an autosomal dominant fashion, ultimately leads to the accumulation of **fumarate**, an oncometabolite, promoting the development of FH-deficient tumors.

GOAL:

To present a case of a patient treated at Centro Hospitalar do Porto diagnosed with HLRCC after a radical nephrectomy due to renal cell carcinoma. Genetic analyses revealed a **novel FH mutation**.

RESULTS:

A 41-year-old female presented to the emergency department with complaints of gross hematuria and right lumbar pain.

As for her medical history, she was taking a beta-blocker due to hypertension and had had a **hysterectomy at age thirty-eight** due to a large uterine myoma that caused severe metrorrhagia. In addition, during her twenties, due to the appearance of abundant **firm skin nodules** on her limbs and back (Fig.1), she had a skin biopsy which reveled the lesions were piloleiomyomas.

In the emergency department, an ultrasound identified a suspicious renal lesion. The subsequent CT scan showed 3 independent renal tumors of the right kidney, with diameters of 4.9, 4.8 and 1.7 cm (Fig.2), with no evidence of metastatic disease. The patient was counseled and had a radical laparoscopic nephrectomy. The pathology examination revealed the renal tumors to be **papillary type 2 renal cell carcinoma** (RCC). Given her previous medical conditions and family history (paternal aunt with papillary type 2 RCC, early hysterectomy and cutaneous leiomyomas, which also afflicted her brother and other family members), her attending urologist suspected of Reed's syndrome. The genetic test revealed a **heterozygous variant (c.322C>T) of the FH locus**, a variant not previously reported in patients with HLRCC . This variant predictably leads to production of a truncated inactive enzyme or none at all.

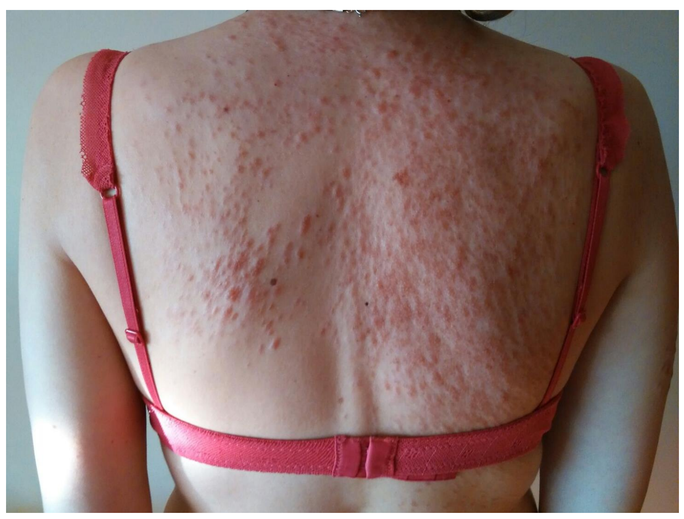

Fig.1 – Photo of the patient presented with cuntaneous piloleiomyomas

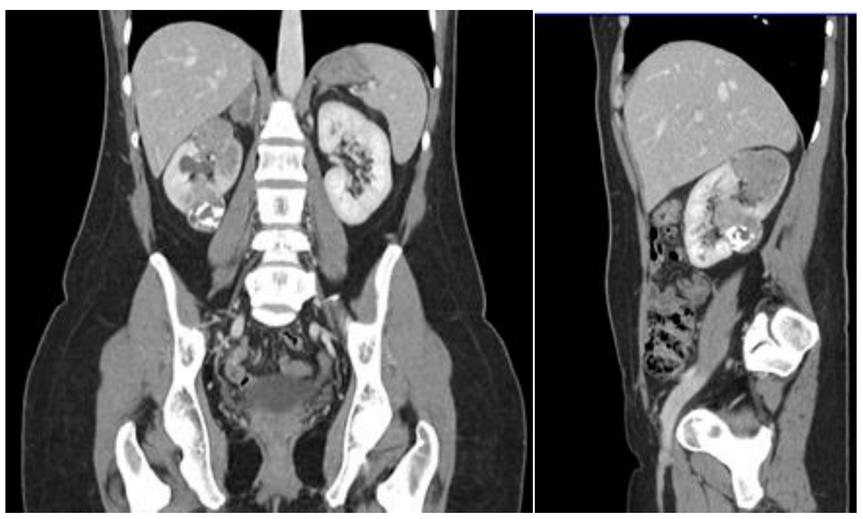

Fig.2 – Patient's initial contrasted CT scan revealing tumors of the right kidney

WHEN TO SUSPECT HLRCC

- **Cutaneous piloleiomyomas:**
  - 76-100% pts with HLRCC
  - multiple firm reddish papula, may be painful
- **Uterine leiomyomas:**
  - 80% females with HLRCC
  - often large, lead to early hysterectomy (average age 35y)
- **Renal cell cancer**:
  - extremely variable prevalance in affected families (average age at diagnosis 41y)
  - mostly unilateral and solitary but with high propensity for early metastization

CONCLUSION:

Diagnosing Reed syndrome is of paramount importance to patients and their family. Retrospective studies of families with HLRCC indicate a **15% cumulative lifetime risk of developing RCC**, a condition that tends to occur in young patients and to metastasize at an early stage. The diagnosis allows for genetic counselling of potentially affected members, family planning in women, and screening for renal tumors, although there is no consensus regarding the frequency or method of screening (US vs RMN).

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