# INTERNAL MEDICINE

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## Renal oncocytoma in a female patient with rheumatoid arthritis and secondary Sjögren's syndrome: Non-coincidental link to autoimmunity?*

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The objective of the article was to describe a female patient with rheumatoid arthritis (RA) and secondary Sjögren's syndrome (SS) who developed a renal oncocytoma and was cured by percutaneous cryoablation therapy. A 72-year-old female patient with a long-term history of polyarthritis involving her hands, shoulders, knees, and ankles associated with morning stiffness and rheumatoid factor of 107 U/mL (nr: <29 U/mL) and anti-CCP of 121 U/mL (nr: <5 U/mL). A diagnosis of RA was determined 10 years ago, and prednisone with methotrexate were initiated, later changed for leflunomide 20mg/day. In 2014 a diagnosis of secondary SS was determined. In April 2014, during a routine abdominal ultrasound, a tumor was found in her left kidney. A magnetic resonance imaging confirmed a solid nodule with hypervascularization on the left kidney. She was submitted to a percutaneous cryoablation procedure without any intercurrence, and it had success. The histopathological analysis demonstrated a renal oncocytoma limited to the left kidney. No chemotherapy or radiotherapy was needed. After surgery, a flare of RA was noted and was resistant to methotrexate and sulfasalazine. Rituximab was then started, and she had an excellent progressive response. Minor thyroid changes were registered by ultrasound monitoring and signs of hyperparathyroidism manifested. This observation illustrates the first ever described case of a patient with RA and secondary SS who developed several years after the RA onset, a renal oncocytoma, and was successfully treated

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with cryoablation therapy. The possible links between oncocytic cell metaplasia/neoplasia and autoimmunity are discussed.

*Keywords:* rheumatoid arthritis, oncocytoma, tumor, neoplasia, metaplasia, dysplasia, autoimmunity, cancer, immunosuppressive drugs, Sjögren's syndrome, Hürthle — Askanazy cells, Hashimoto's thyroiditis.

## Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease, which involves synovial joints. It may lead to articular destruction if not treated and in most cases is characteristic for the presence of autoantibodies towards native nucleohistones/Fc-fragments of immunoglobulins (known as rheumatoid factor, RF) and/or anti-cyclic citrullinated protein (anti-CCP) autoantibodies [1].

RA is associated with an increased incidence of some neoplastic disorders, mainly lymphoid leukemia, lymphoma and also lung cancer. The pathogenesis of this augmented oncological risk is multifactorial and includes shared risk factors (like, smoking for both RA and lung cancer), the presence of chronic inflammation and somatic hypermutation of lymphoid clones involved in autoimmune process, as well as the use of immunosuppressive drugs and biologicals commonly applied in RA [2]. Several other cancers were described in RA, including colorectal, prostate and breast ones, as well as melanoma [3]. But for many cancers no relation to RA was revealed, moreover, the incidence of colorectal cancers in various cohorts of RA patients was even decreased [4–7]. However, to the best of our knowledge, so far no RA case associated with renal oncocytoma was described.

This article aims to report the case of a patient with RA and secondary Sjögren's syndrome (SS) who developed a renal oncocytoma successfully cured by a percutaneous cryoablation procedure.

## Case report

A 72-year-old female patient with arterial hypertension, dyslipidemia, osteopenia and age-related macular degeneration in anamnesis, had hysterectomy due to leiomyoma 20 years ago. She had a long-term history of polyarthritis of her hands, shoulders, knees, and ankles associated with morning stiffness. A diagnosis of RA was determined 10 years ago, and courses of prednisone and methotrexate were initiated, later changed for leflunomide 20mg/day. She came to private clinic in August 2012 with polyarthritis of wrists, left ankle, knees, and second and third metacarpophalangeal joints bilaterally associated with morning stiffness with duration of 5 minutes. Laboratory tests revealed a normal cell blood count, erythrocyte sedimentation rate (ESR) of 90 mm/1st hour, C-reactive protein of 1.8 mg/L (normal range: < 0.1 mg/dL), normal blood biochemical parameters (AST 25 U/L and ALT 15 U/L, gamma-glutamyl transferase 26 U/L), RF of 107 IU/mL (nr: <29 IU/mL) and anti-CCP of 121 U/mL (nr: <5 U/mL). Methotrexate was added to leflunomide in a 15 mg/week dose combined with folic acid 5 mg/week and vitamin $D_3$ 50,000 IU/week. After one month, a marked improvement was observed, no arthritis was noted, and ESR was reduced to 22 mm/1st hour and CRP to 0.1 mg/L with normal blood level of liver enzymes. In October 2013, she experienced diffuse moderate alopecia, and leflunomide was excluded, improving hair problems. In March 2014, she reported xe-

rostomia and xerophthalmia, a Schirmer test showed 8 mm in the left eye and 6 mm in the right eye in 5 min, Bengal rose test was positive, salivary glands scintigraphy was positive, and a diagnosis of secondary Sjögren's syndrome (SS) was determined. In April 2014, during a routine abdominal ultrasound, one tumor was found in her left kidney. A magnetic resonance imaging confirmed a solid nodule with hypervascularization on the left kidney. She was submitted to a percutaneous cryoablation procedure without any intercurrence, and it had success. The histopathological analysis demonstrated a renal oncocytoma limited to the left kidney. No chemotherapy or radiotherapy was needed. After surgery, a flare of RA was noted, and methotrexate was increased to 25mg/week with bad disease control. Sulfasalazine 2g was added, but no response was observed. Anti-CCP was 390 U/mL, RF 256 IU/mL, CRP 6.65 mg/L. She was negative for both anti-thyroglobulin and anti-TPO autoantibodies, and euthyroid, having TSH 0.44 (nr: 0.3–4.0 mU/L) and free T4 1.35 (nr: 0.9–1.8 ng/dL). Although, her thyroid ultrasound revealed a reduced homogeneous gland with a gland volume of 3.6 $cm^3$ (nr: 6–15 $cm^3$) and a nodule of $0.4 \times 0.4 \times 0.4$ cm on the right lobe. In April 2014, due to the recent history of tumor, SS associated, and refractory RA disease activity, rituximab 1 g was initiated and repeated after 15 days. A marked improvement of clinical RA disease activity was seen soon as one month later, and methotrexate was tapered from 20 mg/week to 7.5 mg/week in one year, with normal CRP 0.1 mg/L and ESR 6 mm/1st hour. Rituximab every six months was maintained, and methotrexate was suspended in this period. In September 2018, she presented hypercalcemia of 10.8 mg/dL (nr: 8.5–10.5 mg/dL), associated with a high parathyroid hormone of 136 pg/mL (nr: 10–65 pg/mL), a diagnosis of primary hyperparathyroidism was made, and endocrinologist addressed a conservative approach.

Currently, two years later, the patient is asymptomatic, with RA under control, inflammatory markers are normal, and she is under rituximab every six months. The oncologists considered the tumor cured.

## Discussion

This article is the first description of oncocytoma in a patient with long-term RA and secondary SS.

RA has an increased risk of neoplasia, and the phenomenon is linked to several factors such as aging, drug use, chronic inflammation, and the presence of common risk factors such as smoking, infections, and others. The leading hypothesis is that it is occurring an immunologic stimulus over time, which may increase the risk for malignant transformation of immune cells and reduce the suppressor function of lymphocytes, thus increasing the chance of lymphoma in these subjects [8].

An important risk factor for cancer developing in AR is the use of a TNF blockers. A systematic review that included 123.031 cases indicated that RA individuals treated with these biological drugs are under increased risk of non-melanoma skin cancer (relative risk of 1.28; 95 % CI: 1.19–1.38, P = 0.056) [9]. Besides, the presence of autoantibodies seems to be also a risk factor for cancer in these RA patients. Confirming this hypothesis, a population-based case-control study linked to the Swedish nationwide cancer register showed an amplified risk for lung cancer in RA patients who were positive for rheumatoid and/or anti-CCP antibodies [10]. It is important to emphasize that our patient had both these autoantibodies positive.

SS is an autoimmune disease characterized by sicca syndrome, autoantibodies to some ribonucleoproteins and high risk of neoplasia. In a metanalysis including 14 studies with a total of 14.523 patients, the authors found an increased overall cancer risk (pooled RR 1.53; 95 % CI 1.17 to 1.88), and risks of non-Hodgkin lymphoma (NHL) (pooled RR 13.76; 95 % CI 8.53 to 18.99) and thyroid cancer [11]. However, no case of SS associated with renal oncocytoma was described so far.

Oncocytoma is tumor of low or no malignancy (carcinoma or adenoma) that has some challenges in its diagnosis. Usually, it is asymptomatic neoplasm, often discovered incidentally on cross-sectional imaging performed for other clinical indications [12], as it happened in our patient.

Neoplastic process goes in multi-step sequence of somatic mutations, hence metaplasia and dysplasia of epitheliocytes in parenchymal organs may form oncocytoid foci, which precede oncocytomas [13]. Most often such oncocytoid dysplasia and oncocytomas are located in thyroid gland, but sometimes they may occur in kidney, parathyroid, liver or very seldom — in other organs [14; 15].

To our opinion, the comorbidity of oncocytoma with two autoimmune diseases in one individual, described in this case, is remarkable and non-coincidental.

The source of oncocytomas is a mutant clone of oncocytes, having a series of somatic mutations in mitochondrial DNA, altering the sub-units of oxidative phosphorylation complexes I and IV and ATPase–6 variant. The oxidative function in oncocytes is diminished, triggering a compensatory mechanism of increased mitochondrial biogenesis. Because of that, their granular, brightly eosinophilic, swollen cytoplasm is loaded with large dysplastic mitochondria [14].

Cells with oncocytic phenotype (possibly, of parafollicular origin) were first described in 1894 by Karl Hürthle (1860–1945) in canine thyroid gland [16], but four years later Max Askanazy (1865–1940) have shown the abundance of follicular oncocytes in human thyroid, in patients with Graves'–von Basedow disease [17]. Most probably, Askanazy's cases were that of hashitoxicosis, because currently oncocytes or Hürthle — Askanazy cells (which are very rare in normal thyroid) are recognized as very typical for Hashimoto's autoimmune thyroiditis and even prominent in this particular disorder, being one of its key pathomorphological sings, with majority of follicular thyrocytes showing this particular kind of metaplasia. That fact was noticed even in very first description of the Hashimoto's disease and still considered to be important [18–20]. Oncocytes also are common elements of thyroid Hürthle cell tumors and present in some papillary and follicular thyroid cancers [13]. Oncocytes, both in autoimmune thyroiditis and in oncocytomas express plenty of thyroid peroxidase in abnormal mitochondrial location [21; 22]. They also express neuron-specific enolase, both enzymes targeted by autoimmune process in Hashimoto's thyroiditis [23; 24]. Chaperonin HSP60, involved in pathogenesis of several autoimmune diseases, is hyperexpressed by oncocytes, it presents on their plasma membrane and displays cross-reactivity both with thyroglobulin and thyroid peroxidase [25]. There is even a hypothesis that oxidative damage of these enzymes in dysfunctional mitochondria of oncocytes along with disorder of apoptosis control — may serve as primary lesion precipitating subsequent chronic autoimmune process [16]. Oncocytes in Hashimoto's disease lack of the oxidative phosphorylation complex I, which is a target of T-killer cells apoptogenic attack, thus having a selective advantage and surviving under lymphocyte infiltration conditions [22].

It has been shown that oncocytic metaplasia is the result of an increased immunoproteasome expression in oncocytes, which additionally linked this cell transformation to autoimmune and autoinflammatory processes [26].

In our patient, the oncocytoma was located in kidney. Renal oncocytoma, first described in 1942 by L. Zippel [27] earlier also was related to immunopathological glomerular changes typical for autoimmune glomerular disease [28]. Oncocytomas are as a rule indolent and if non-diagnosed may grow up to giant weight (2–4.6 kilos) [29]. In our case because of relatively early occasional diagnosis a tumor however have reached just small size.

Perhaps, in this case systemic autoimmune diseases and oncocytoma were mechanistically linked. Indeed, we detected a very small thyroid gland in our patient though, in line with our hypothesis of a realtionshib among these diseases [19]. The subsequent manifestation of hyperparathyroidism in our patient could be related to parathyroid adenoma, which also often may be oncocytic and even intrathyroid-located [30]. It raises a question of possible nature of a thyroid nodule revealed in our patient. For parathyroid tumors association between autoimmune lesion and oncocytic transformation of cells has been confirmed as well [31]. Alternative point of view on oncocytic transformation is based on the fact that prevalence of Hürthle — Askanazy cells in Hashimoto's thyroiditis is progressively increasing with every decade of patient's age, being non-typical for its pediatric cases. Thus, their "hürthlization" can be regarded as survival reaction resulted from chronic immunopathological process and auto-aggression [32].

Hence, in our case of chronic systemic autoimmune diseases, like SS and RA, oncocytic metaplasia and dysplasia as a step towards oncocytoma also could be a result of epithelial cell survival reaction for autoimmune aggression and/or facilitate autopresentation of the antigens abundant in oncocytes.

Recently a case of renal oncocytoma positive, for alpha-enolase combined with autoimmune retinopathy and optic neuropathy was reported [33]. Oncocytomas have been repeatedly reported in association with various cases of autoimmune diseases, not only thyroid ones [34], but also bullous pemphigoid [35], and multiple sclerosis [36]. In autoimmune diabetes mellitus type 1 there is a cross-reactivity between VP1 capsid protein of provoking enterovirus and mitochondrial proteins of oncocytoma cells [37].

Taken together, all these observations witness for non-occasional link(s) between oncocytomas/oncocytoid metaplasia of epithelial cells and autoimmunity.

The cryoablation procedure is an approach used to cure oncocytoma, commonly for benign conditions such as cryoablation after a congelation biopsy with a low risk of complications [38]. However, complications are linked with this procedure, such as ureteral obstruction months after the surgery [39].

In **conclusion**, the present case brings other neoplasia associated with RA/SS patients, to our knowledge never described in literature before. Physicians should be alert to an incidental mass found in abdominal imaging studies in their patients. Nevertheless, oncocytic metaplasia, dysplasia and oncocytomas are related to several autoimmune disorders, and in our patient their comorbidity is, most probably, non-coincidental, because they have common links of pathogenesis.

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## Ethical statement

The authors declare that they followed the World Medical Association Declaration of Helsinki in this study. An informed consent was obtained from the patient for publication of the case. No images or other identification data of the patient were used.

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