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A case of renal cell carcinoma metastases to the neck after long-term latency in the setting of chronic lymphocytic leukemia progression

Ewa Zabrocka[1], Ewa Sierko[1,2], Marek Z. Wojtukiewicz[1,2]

[1] Department of Oncology, Medical University of Bialystok, Poland; [2] Comprehensive Cancer Center in Bialystok, Poland

Summary. We report on a 71-year-old man with a three-year history of chronic lymphocytic leukemia (CLL) who underwent left-sided nephrectomy due to renal cell carcinoma (RCC) 16 years earlier. Because of the CLL progression, he was being treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) regimen, when he started to complain of hoarseness and cough. Laryngological examination disclosed tumorous lesion involving right half of the larynx. On computed tomography (CT) scans numerous lesions in the neck region (e.g. larynx, thyroid gland) were revealed. RCC metastases were confirmed in the histopathological examination of the specimen from the larynx. Since the treatment with interferon alpha was intolerable, eight courses of multi-kinase inhibitor, sorafenib, were applied. Despite the initial regression, progressive disease was shown in post-treatment CT. At present, the patient is being treated with m-TOR inhibitor, everolimus.

Key words: cancer dormancy, second malignancy, targeted therapy, late metastatic disease, lymphoid malignancy

Background

Renal cell carcinoma (RCC) is considered to have an unpredictable clinical course due to its potential to metastasize even many years after radical treatment, sometimes with the involvement of unusual sites. Late recurrence was observed in almost 7% of patients who had been disease free for ≥10 years after nephrectomy (1).

Second primary malignancies have been described in numerous tumors. The incidence of RCC with lymphoid malignancy was found to be higher than expected in general population (2). However, the reports on the coexistence with chronic lymphocytic leukemia (CLL) are rare (3). The more unusual is the occurrence of RCC metastases to the neck region in the setting of CLL progression, many years after curative nephrectomy. We present a patient with such an uncommon clinical history.

Case presentation

A 71-year-old man, diagnosed with chronic lymphocytic leukemia (Rai III) 3 years earlier, was treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) due to the disease progression. The patient's medical history was notable for chronic atrial fibrillation, rheumatoid arthritis, ischemic stroke at age 52 and left-sided nephrectomy because of renal clear cell carcinoma (G2, pT2) at age 55. He completed the third course of R-CHOP when he complained of a persistent hoarseness and hacking cough. An exophytic ulcerated tumor involving right half of the larynx was disclosed in the laryngological examination. The histopathological study of collected specimens revealed the infiltration of the larynx with clear cell carcinoma, most likely of renal origin. Since the rima glottidis was very narrow, a tracheostomy with tube insertion was performed. In head and neck (H&N)

computed tomography (CT) scans numerous nodules within and around the thyroid gland, most probably metastases, were visualized. The gland itself was enlarged and bulging into the lumen of trachea. The tumorous lesions were also bulging into right common jugular vein and infiltrating the vocal chords. Additionally, there were numerous, similarly enhancing focal changes scattered around trachea and within soft tissues of the neck (Fig. 1A). An abdominal CT was unremarkable.

A treatment with interferon alpha was commenced, however it had to be stopped after the first course because of unbearable side effects. Since the patient was eligible for a sorafenib (800 mg per day) treatment program, the second-line therapy with sorafenib was implemented. The first course was complicated with dysuria and hand-foot syndrome (grade 2). The adverse symptoms resolved upon an appropriate management and did not interrupt the primary treatment. A CT performed after the first cycle shown a regression of the neck lesions. The lesions were stable in control CT scans after the fifth course. In total, eight continuous courses of sorafenib, each 28-day-long, were administered. Post-treatment CT disclosed progression of the lesion above the tracheostomy tube, bulging into the trachea and virtually closing its lumen. Again, an abdominal CT was unremarkable. Since the patient met the inclusion criteria for a treatment program with everolimus (10 mg per day), the therapy was commenced. CT of the neck performed after two courses showed the lesions were stable (Fig. 1B). The treatment was withheld for two weeks between second and third course due to the bleeding from tracheostomy tube and worsening of blood morphology (hemoglobin 9.69 g/dl). After completion of the third course, pneumonia had developed along with hyperosmolar hyperglycemic state, secondary thrombocytopenia, anemia and neutropenia. By now, the patient has been recovering and the treatment with everolimus has been withheld.

Discussion

At the time of diagnosis, 30% of RCC patients have metastases, most commonly to the lungs, bones, liver and brain. Of the patients after radical nephrectomy, another 30% will experience local or distal recurrence (4). Among other tumors, RCC is known for its potential to metastasize to unusual sites, even years after the diagnosis. Deeb et al (5) reported on a case of RCC metastasis to parotid gland almost two decades after RCC diagnosis and radical treatment. H&N region, however, is quite uncommon site for RCC metastasis, accounting for 8-14% of metastatic regions, with thyroid involvement as the most prevalent (6). Reports on metastases to the larynx are rarely encountered. Regarding metastatic RCC, our case is not only distinctive of the H&N involvement itself, but it also stands out with several rarely affected sites: the larynx, the thyroid gland, perilaryngeal and perithyroidal ar-

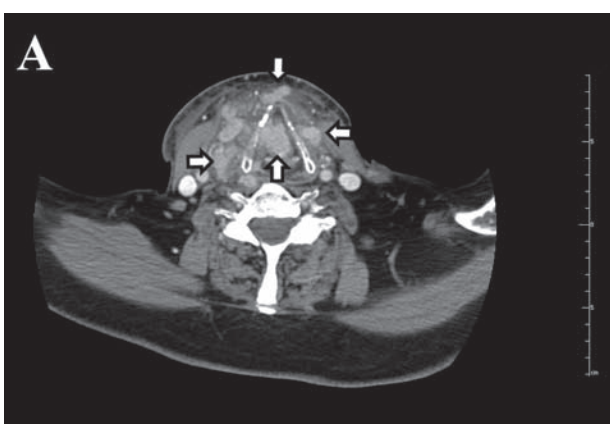

Figure 1A. Computed tomography of the neck before treatment. RCC metastases to the larynx, the thyroid gland, peritracheal area and to the soft tissues of the neck.

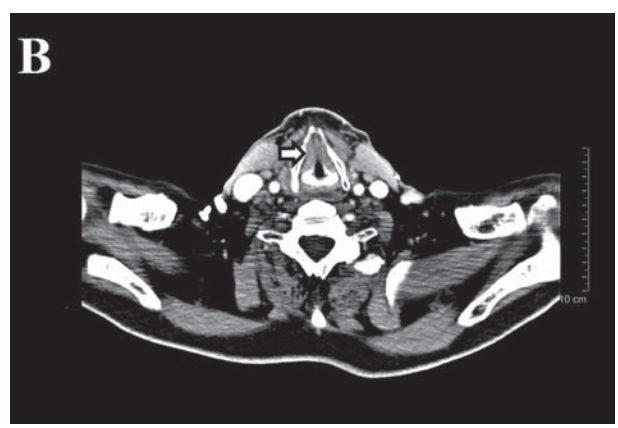

Figure 1B. Computed tomography of the neck after two courses of everolimus. Stabilization of the metastatic lesions.

eas. The mechanism of RCC spread to H&N region could be explained by its hypervascular nature and venous anastomoses between the vertebral and epidural systems. As intraabdominal pressure rises, the retrograde flow through the shunting system supports bypassing pulmonary filter bed, thereby enabling RCC spread to H&N (7).

However, the presentation of RCC metastases after long latency from a curative treatment and shortly after CLL progression is peculiar. Possible cause that could underlie this phenomenon is previous cancer dormancy with subsequent switch from a dormant to proliferative state. Since the immunosurveillance may be involved in cancer dormancy (8), the immune system impairment during the CLL progression could trigger the metastases disclosure. Also the influence of rituximab should be considered. Since B cells were found to present antitumor activity (9), the B-cell depletion and secondary immunosuppression by rituximab could play a role. The immunodeficiency is also induced by chemotherapy and glucocorticoids used in CLL treatment regimens.

An occurrence of both CLL and RCC in our patient is particularly interesting. The risk of non-Hodgkin lymphoma (NHL), including CLL, in RCC patients, expressed as observed to expected ratio, was shown to be increased one year onwards after RCC diagnosis, although the ratio was statistically significant only between 2 and 5 years of follow-up (10). Likewise, Nishikubo *et al.* (2) found the incidence of lymphoid malignancy with RCC was higher than expected in general population. The development of a secondary CLL could be either related to the immune system defect or its dysregulation caused by the first neoplasm. Production of tumor-stimulating substance by the first tumor is also possible, although seems to be unlikely in the cases of long time interval between the onsets of two malignancies. Also common mutations of chromosomes 3p and 17p, found in both RCC and NHL (11), could suggest a common pathogenesis of these malignancies. Treatment-related development of a second malignancy in RCC patients is questioned. Among patients from a case series reported by Nishikubo *et al.* (2) diagnosed with RCC first, hematological malignancies occurred despite the only treatment modality was nephrectomy (without chemo- or radiotherapy).

Conclusions

It is of particular importance for physicians to be aware that any patient with a history of RCC is at risk for metastatic disease even many years after diagnosis, including uncommon sites. A long-term surveillance should be considered. Given that the pathological mechanisms underlying the co-occurrence of hematological malignancies and RCC have not been discovered, further studies are warranted.

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Address: Ewa Sierko
Department of Oncology, Medical University
12 Ogrodowa Street, 15-027 Bialystok, Poland
Tel. (+48) 85 6646753
Fax (+48) 85 6646711
E-mail address: ewa.sierko@iq.pl