CLINICAL CASE

Hemolytic anemia as paraneoplastic syndrome in renal cell carcinoma


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KEYWORDS
Hemolytic anemia; Paraneoplastic syndrome; Clear cell renal cell carcinoma; Mexico.

Abstract  Tumor processes can first manifest with nonspecific symptomaticology not caused by local invasion or metastasis. This is referred to as paraneoplastic, and can appear years before the typical tumor symptoms. These types of initial manifestations can be key to the discovery of an occult tumor. Renal cell carcinoma can cause various signs and symptoms of a paraneoplastic syndrome, ranging from constitutional symptoms (fever, weight loss) to biochemical, metabolic, and hematologic disorders. For these reasons this tumor became known as “the great masquerader in medicine”, given its capacity to affect almost all organs and systems. It has been estimated that approximately one third of affected patients show signs and symptoms of paraneoplastic syndrome.

The aim of the present article was to show that the hematologic changes suggestive of hemolytic anemia can be the first manifestation of a paraneoplastic syndrome associated with renal tumor.

The appearance of hematologic alterations suggestive of hemolytic anemia can be the first and only manifestation of renal carcinoma, and an occult tumor should be suspected in patients with such alterations. The diagnosis of hemolytic anemia as paraneoplastic syndrome should be made by exclusion, after ruling out other causes such as primary hematologic alterations, metastasis, or vascular processes.
Introduction

Tumor processes can present their first manifestations as non-specific alterations, not originating from local invasion or metastasis, but rather from the so-called paraneoplastic syndromes that can appear much before the customary tumor symptoms. These initial manifestations can be key in discovering an occult neoplasia.

Renal cell cancer is the most frequent solid renal tumor in adults and represents 2.3% of all malignant tumors. It is more frequent in men than in women (3:1), especially between the ages of 50 and 70 years; the mean age is 65 years.

Almost all primary tumors are associated with paraneoplastic syndromes and the most frequent are small cell lung cancer, breast cancer, gynecologic cancers, and lymphomas. With respect to renal cell carcinoma, it has been estimated that one third of affected patients show signs and symptoms of paraneoplastic syndrome, from constitutional symptoms (fever, weight loss) to specific metabolic, hematologic, and biochemical disorders.

This cancer can increase the secretion of certain hormones produced by the kidney, causing the so-called paraneoplastic syndromes, such as: hypercalcemia due to ectopic hyperparathyroidism (an increase in PTH); polycythemia (an increase in red blood cells) due to elevated erythropoietin secretion; high blood pressure due to the release of renin or renal artery compression; Cushing’s syndrome due to ectopic secretion of ACTH; galactorrhea due to ectopic secretion of prolactin; and gynecomastia due to ectopic secretion of gonadotropin.

The diagnosis of paraneoplastic syndromes should be made after ruling out metastases, infections, metabolic processes, and vascular alterations.

Treatment of paraneoplastic syndromes is directed at the disease that causes them, in other words, the tumor. On certain occasions, when the underlying disease cannot be treated, then the symptoms and complications caused by the paraneoplastic syndrome should be. This symptomatology can be much more important that that caused by the primary tumor.

Paraneoplastic syndromes tend to return when the underlying disease is controlled, but in certain cases its progression can be independent from the primary tumor.

Case presentation

A 71-year-old woman had a past medical history of diabetes and high blood pressure with adequate control. Disease began 6 months before with fatigue, slow gait, hyporexia, intermittent fever, respiratory difficulty, and a sudden generalized jaundice one month prior. Physical examination revealed jaundiced skin and sclera, normal cardiopulmonary data, a soft and depressible abdomen with present peristalsis, non-palpable kidneys, and negative left costovertebral angle percussion. Full blood count reported leukocytes 3.7, neutrophils 2.10, lymphocytes 1.60, hemoglobin 6.7, hematocrit 19%, platelets of 70,000; direct bilirubin (DB) 0.62, indirect bilirubin (IB) 2.11, total bilirubin (TB) 2.73, and lactate dehydrogenase (LDH) 91. The patient had a transfusion of 2 red cell packs, antibiotic therapy was begun with levofloxacin, and she presented with an elevation of hemoglobin to 7.2 g, leukocytes 4.1, neutrophils 2.3, lymphocytes 1.8, hematocrit 22%, and thrombocytopenia 66,000, as well as increased liver enzymes. The patient was evaluated by the Hematology Service and a blood smear reported macrocytosis, basophilia, and thrombocytopenia. LDH remained elevated, IB 2.3, positive direct Coombs with a 1:16 dilution, and haptoglobin of 26 mg/dL. During her hospital stay, the patient presented with diffuse abdominal pain and a computed axial tomography (CAT) scan revealed a 6 cm left renal tumor that was dependent on the upper pole, with areas of necrosis in the simple phase, and 6 HU increasing to 40 HU.
with no vascular involvement. Her hematologic conditions improved with a transfusion of 4 red cell packs and left radical nephrectomy was performed with no complications. The hematologic parameters improved 3 days after the surgical procedure with hemoglobin at 9.9 g, hematocrit 29%, leukocytes 6.6, lymphocytes 0.56, and platelets 98,000. The last control was carried out 3 months later with hemoglobin of 12.1 g, hematocrit 43%, leukocytes 5.3, neutrophils 4.4, lymphocytes 0.60, and platelets 130,000.

Histopathologic report: Well differentiated, 4 x 3.5 cm, clear cell carcinoma, Fuhrman I, T1aN0M0, located in the upper renal pole and confined to the renal parenchyma.

Discussion

Tumor processes can initially show hematologic alterations due to the release of characteristic substances of the tumor, metastases, or to presenting as paraneoplastic syndrome. There are very few cases in the medical literature on hematologic alterations associated with renal tumor metastasis. In the present case, the hematologic involvement was not due to metastasis, but rather to a paraneoplastic syndrome, given that the first manifestation found was thrombocytopenia with jaundice secondary to hemolysis.

Paraneoplastic syndromes involve organs and tissues that do not have anything to do with the primary tumor or its metastasis and they can affect the majority of organs and tissues of the organism. Most symptoms are produced by immunologic mechanisms that produce an autoimmune degeneration at the hematologic level. Just as in the case presented herein, when the paraneoplastic syndrome appears the tumor can still be asymptomatic; the hematologic alterations can precede the tumor diagnosis to the point that they cause clinical signs and symptoms (jaundice, asthenia, adynamia), which lead the patient to medical consultation and can be the key to diagnosing the occult tumor.

Almost all primary tumors can cause paraneoplastic syndromes and the most frequent is small cell lung cancer. In regard to renal cell carcinoma, it has been estimated that approximately one third of affected patients show signs and symptoms of paraneoplastic syndrome, encompassing both constitutional symptoms (fever, weight loss) and specific metabolic and biochemical disorders (hypercalcemia, high blood pressure, polycythemia, non-metastatic hepatopathy, amyloidosis, galactorrhea, Cushing’s syndrome, hyper or hypoglycemia, among others) and therefore this tumor has been called “the great masquerader of medicine”, given its capacity to affect all organs and systems. In relation to the hematologic involvement, the associated paraneoplastic symptoms can include very diverse manifestations, such as thrombocytosis or thrombocytopenia.

The association of a paraneoplastic syndrome can provide various aspects of practical interest. Its presence is not a marker for the existence of metastasis, nor does it indicate a worse outcome, but if at a certain moment there is a recurrence of a previous paraneoplastic syndrome, this should be a red flag for the possibility of tumor process progression. In other situations, such as the present case, the appearance of paraneoplastic syndrome can be key in initiating the search for an occult tumor. However, in up to 20% of the cases of patients with paraneoplastic tumor, it is not possible to confirm the presence of tumor, even after autopsy.

Renal carcinoma rarely is associated with hematologic paraneoplastic syndrome, but, as in our case, the appearance of a hematologic syndrome can be the first and only manifestation of a renal carcinoma, even years before the first urologic manifestations.

The clinical presentation of renal carcinoma can be diverse; the cancer can remain silent and be discovered incidentally, it can produce alterations due to the expansive renal process itself, or present with clinical manifestations derived from metastases or paraneoplastic syndromes. These latter present in more than 20% of the renal carcinomas and in some of the cases are the initial manifestation. This situation was what led to the study and posterior diagnosis of our patient.

The pathogenesis of these paraneoplastic syndromes consists of the release of substances with endocrine and metabolic action by the tumor cells, or that they induce the release of inflammation mediators, principally interleukins or cytokines. IL-6 has been identified as being responsible for some processes.

The diagnostic process of renal carcinoma has notably varied over the last few years, and incidental diagnosis is increasingly more frequent during complementary examinations of unrelated diseases or in routine sonography. Our case cannot be strictly considered incidental because the patient already presented with paraneoplastic hematologic manifestations that motivated its study, producing a primary occult tumor.

Conclusions

There are different solid tumors that can be preceded by some type of hematologic paraneoplastic syndrome. The appearance of hematologic alterations suggestive of hemolytic anemia can be the first and only manifestation of a renal carcinoma and an occult tumor should be suspected in patients presenting with these hematologic alterations. The diagnosis of hemolytic anemia as a paraneoplastic syndrome should be reached by exclusion, ruling out other causes such as primary hematologic alterations, metastasis, or vascular processes. The treatment of paraneoplastic syndromes is directed at the disease that causes them, the tumor.

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Conflict of interest

The authors declare that there is no conflict of interest.

References