Acquired Ichthyosis as the Primary Manifestation of Renal Cell carcinoma

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The term ichthyosis is derived from *ichthys*, the ancient Greek root meaning fish, and refers to the similarity in appearance of the skin to fish scales. The ichthyoses are a heterogeneous group of cutaneous keratinization disorders, with both inherited and acquired forms. The acquired form has been associated with systemic diseases, including malignant, infectious, autoimmune and endocrine disorders, as well as metabolic conditions and medications. Malignancy accounts for half of the reported cases, most commonly as lymphoproliferative disorders. We report a patient who presented with widespread ichthyosis as the primary manifestation of renal cell carcinoma, an association that has not been reported previously.

PATIENT DESCRIPTION

An 81 year old man presented with a 2 month history of a pruritic skin eruption. His medical history revealed hypertension, congestive heart failure, moderate chronic renal failure and hypothyroidism, which were all well controlled. There was no personal or family history of ichthyosis. Physical examination disclosed marked confluent widespread scaly rash distributed on his scalp, forehead, eyelids, cheeks, the trunk and the extremities. Bilateral ectropion due to eyelid involvement with ichthyosis was present. The extensor surfaces of the extremities were mainly involved, sparing the flexor surfaces. A clinical diagnosis of acquired ichthyosis was made by two expert dermatologists. Skin biopsy was not performed as the rash showed typical features of ichthyosis and it was felt that it would not add to the existing diagnosis.

Evaluation for an underlying malignancy using an abdominal computed tomography scan revealed an enlarged left kidney with a solid 4 cm mass. The patient underwent left radical nephrectomy and the histopathological examination of the mass specimen was consistent with renal cell carcinoma, clear cell type, grade 2. Two months after surgery there was significant improvement of the skin lesions, mainly on the scalp and face, confirming the association between the tumor and ichthyosis.

COMMENT

The ichthyoses are a heterogeneous group of cutaneous keratinization disorders, distinguished clinically by generalized scaling. The focal point of abnormality in all ichthyoses is the stratum corneum. In ichthyotic skin there is thickening of the stratum corneum as a result either of cells entering the compartment at an increased rate (hyperproliferation) or leaving (corneocytes disadhesion) too slowly, or both. The ichthyotic skin has an abnormal quality and quantity of scale, and the barrier function of the stratum corneum is compromised [1]. A PubMed literature search on acquired ichthyosis from 1951 to 2007 showed that it has been reported in association with a variety of diseases including malignancy, infections, autoimmune and endocrine diseases, as well as metabolic conditions, medications and others [Table]. Malignancy was the cause of acquired ichthyosis in nearly half the case reports identified. One-third of the cancer reports were related to Hodgkin's disease, the most common disease reported with acquired ichthyosis. Other lymphoproliferative diseases reported with acquired ichthyosis include mycosis fungoides, non-Hodgkin's lymphoma, anaplastic large cell lymphoma and lymphomatoid papulosis. Acquired ichthyosis was also reported in association with other hematological malignancies, including multiple myeloma, polycythemia vera, adult T cell lymphoma/leukemia, malignant histiocytosis, POEMS syndrome and myelodysplastic syndrome. Reported solid tumors associated with acquired ichthyosis include breast, bronchial, laryngeal, esophageal, gastric,

Malignant diseases reported with acquired ichthyosis

Malignant diseases		
Hodgkin's lymphoma	POEMS syndrome	Ovarian tumor
Mycosis fungoides	Myelodysplastic syndrome	Cervix carcinoma
Non-Hodgkin's lymphoma	Breast carcinoma	Kaposi's sarcoma
Anaplastic large cell lymphoma	Bronchial carcinoma	Intestinal leiomyosarcoma
Lymphomatoid papulosis	Laryngeal carcinoma	Rhabdomyosarcoma
ATL (adult T cell leukemia/lymphoma	Esophageal carcinoma	Granulocytic sarcoma
Polycythemia vera	Gastric carcinoma	Reticulum cell sarcoma
Multiple myeloma	Hepatocellular carcinoma	Spindle cell sarcoma
Malignant histiocytosis	Bladder carcinoma	Malignant melanoma
	Transitional cell carcinoma of kidney	

bladder, transitional cell carcinoma of kidney, cervix, and ovarian cancer. The reported sarcomas include Kaposi's sarcoma, leiomyosarcoma, rhabdomyosarcoma, reticulum cell sarcoma, and granulocytic sarcoma. Overall, hematological malignancies account for 60% of the reported cases of acquired ichthyosis associated with malignant diseases, while solid tumors account for 25%, and sarcomas for 15%. Acquired ichthyosis has rarely been described in bone marrow transplant recipients for leukemia and it is associated with additional features of graft-versus-host disease of the skin.

Our case of acquired ichthyosis associated with renal cell carcinoma is unique since such an association has not been reported previously. A variety of paraneoplastic syndromes have been associated with renal cell carcinomas, including erythrocytosis, hypercalcemia, non-metastatic hepatic dysfunction (Stauffer's syndrome), and acquired dysfibrinogenemia. On the other hand renal cell carcinoma is not commonly associated with paraneoplastic mucocutaneous manifestations [2], and only a few cases have been reported, including pemphigus, urticarial vasculitis [3] and erythema gyratum repens [4]. The fact that removal of the malignant tumor resulted in significant improvement of the ichthyotic rash further supports the connection between the rash and this type of malignancy.

Acquired ichthyosis may precede the diagnosis of the underlying malignancy with a 2 week to 10 year interval between presentation and diagnosis of the underlying disease. Prolonged intervals were especially documented in the lymphoproliferative diseases. It is uncommon for paraneoplastic acquired ichthyosis to occur as the sole manifestation of the underlying disease; in most cases it occurs simultaneously with additional cutaneous or systemic manifestations. The common associated systemic manifestations are weight loss, fatigue and lymphadenopathy. Most cases present with symmetric generalized ichthyotic non-pruritic eruption involving both the upper and lower parts of the body, with some predilection for the upper extremities. The pathophysiological mechanisms responsible for paraneoplastic ichthyosis are far from clear. The process of cornification is complex and not completely understood, and defects in many different aspects and steps of this process can lead to a similar end result: abnormal stratum corneum, scale, and hyperkeratosis. Cooper et al. [5], who measured dermal and epidermal lipid biosynthesis by radiolabeled glucose incorporation into lipids, found low epidermal lipid labeling in one patient with Hodgkin's disease and severe ichthyosis, suggesting impaired epidermal lipogenesis as the mechanism of the cutaneous changes in acquired ichthyosis. Transforming growth factor-alpha produced by tumor cells has also been implicated in the pathogenesis of paraneoplastic acquired ichthyosis. Treatment of the underlying malignant disease results in healing of ichthyosis in most cases within 1–6 months, as occurred in our case.

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