Response to Chemotherapy of Paraneoplastic Erythroderma in a Patient with Ovarian Cancer

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ABSTRACT
Background: Erythroderma may be secondary to several skin diseases, drug reactions, infections, and internal malignancies. Skin lesions usually have an unfavorable course until the underlying disease is treated, therefore a thorough search for the cause of erythroderma is mandatory.

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**BACKGROUND**

Erythroderma is an uncommon potentially fatal skin disorder first described by Hebra in 1868. Erythroderma is a definitive term that refers to generalized erythema and desquamation affecting > 90% of the body surface. It usually occurs in individuals older than 40, except when the subjacent disease is atopic dermatitis, seborrheic dermatitis or hereditary ichthyosis [1,2]. Erythroderma represents a reaction pattern, a maximal form of skin irritation that may be secondary to certain cutaneous diseases, drug reactions, infections, solid or hematological malignancies, and other conditions. In the absence of a suggestive history, the clinical and histopathologic distinction between the underlying causes is often problematic and determining the specific etiology is very challenging, an important proportion of cases being classified as idiopathic erythroderma.

Paraneoplastic erythroderma can predate, occur simultaneously with or follow the detection of an internal malignancy (breast cancer, gastric cancer, colon cancer, gallbladder cancer, small cell lung cancer, head and neck cancer, lymphoma [3-5]). Ovarian cancer is rarely associated with erythroderma.

**CASE REPORT**

We present the case of a 51-year-old female patient who was admitted to our clinic for erythroderma of unknown etiology of 6 months duration. Extensive screening for the cause of erythroderma lead to the diagnosis of left ovarian papillary serous carcinoma invasive to the epiploon, parietal peritoneum and the wall of the urinary bladder, stage IIC FIGO, pT2c pN0 cM0. The patient underwent surgery, followed by multiple lines of chemotherapy. Whole body computed tomography scan, measurement of serum levels of tumoral markers and dermatologic reevaluation were performed every 3 months.

**Results:** The course of skin lesions paralleled that of the subjacent malignancy and was most favorable under platinum plus gemcitabinum and platinum plus taxanes based chemotherapy that also best controlled the neoplastic process.

**Conclusion:** The parallel evolution of the ovarian carcinoma and cutaneous lesions firmly supports the diagnosis of paraneoplastic erythroderma in our patient. Screening for internal neoplasia should be performed in all cases of erythroderma of unknown etiology.

**Key words:** erythroderma, ovarian cancer, chemotherapy

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Laboratory work-up showed important eosinophilia (22.9%, normal values <7%), increased lactate dehydrogenase level (1094 U/l, normal value < 220 U/l), inflammatory syndrome (erythrocyte sedimentation rate = 67 mm/h, normal value < 20 mm/h; C reactive protein = 18.8 mg/l, normal value < 5 mg/l), and a high serum immunoglobulin (Ig) E level (1019 UI/ml, normal value <100 UI/ml). Abdominal ultrasound indicated the presence of a left ovarian tumor. Computer tomograph scan confirmed the existence of a large left ovarian tumor (10.5/9.2/10cm) and subdiaphragmatic adenopathy. CA 125 value was 91.7 UI/ml (normal values < 35 UI/ml). A new skin biopsy was performed and the histopathologic exam showed an interface dermatitis.

The patient was referred to a gynecology specialist. Intraoperative examination revealed left ovarian tumor invasive to the epiploon, parietal peritoneum and the wall of the urinary bladder and total hysterectomy with bilateral adnexectomy, inguinal lymph node dissection and omentectomy was performed. The histopathologic and immunohistochemical diagnosis was G3 papillary serous ovarian carcinoma (ER+80%, PGR+90%, Ki 67+60%), pT2c pN0 cM0 stage IIC.

The oncology specialist initiated treatment with paclitaxel 175mg/m2 IV and carboplatin AUC6 day 1, every 3 weeks. After 3 cycles of chemotherapy, the patient experienced significant improvement of the skin lesions and well circumscribed areas of normal skin appeared on the patient’s torso. Topical treatment consisted of intermediate-strength topical steroids and emollients. However, the skin lesions gradually worsened.

After 6 cycles of paclitaxel and carboplatin, the values of tumoral markers were within normal limits, but positron emission tomography showed the presence of multiple peritoneal, supra- and subdiaphragmatic lymph node metastases. Surgical re-intervention, consisting of omentectomy, pelvic, right prerenal, and right subdiaphragmatic peritoneectomy with diaphragm parcelar resection, right pleurostomy and left external iliac and interaortocaval lymphadenectomy was performed. Histopathologic exam of the peritoneal nodules and epiploon revealed the presence of G3 papillary serous carcinoma. The oncology tumor board initiated second line therapy with topotecan 1.5 mg/m2/ dayIV, days 1-5, every 21 days for 6 cycles.

CT scan showed disease progression, with increase in the number and size of peritoneal and retroperitoneal lymph nodes metastases. The medical oncologist decided to stop treatment with topotecan and to start administration of liposomal doxorubicin 50 mg/m2 IV, every 28 days. After the fourth cycle of treatment with liposomal doxorubicin, the patient presented with grade III oral mucositis. Whole body CT scan described the appearance of a pleural metastasis, an increase in CA125 level and the bone MRI scan showed T9 bone metastases. The skin lesions showed no improvement and the tumor board concluded that during the course of the illness, the paraneoplastic skin lesions only improved under platinum based chemotherapy. Therefore, treatment with gemcitabine 1000mg/m2 IV days 1,8 and carboplatin AUC4 IV day 1 plus zoledronic acid 4mg day 8, every 21 days was initiated and after 10 cycles the CT scan showed a partial response for the first time in 2 years of chemotherapy. The course of skin lesions paralleled that of the subjacent malignancy and significant improvement of the cutaneous manifestations was observed upon dermatologic reassessment (Fig. 2).

DISCUSSION

Ovarian cancers are the ninth most common cancers in women, accounting for approximately 3%
of all new malignancies in women and are frequently diagnosed in an advanced stage [6]. Ovarian cancer can be associated with several paraneoplastic syndromes, including nervous system disorders (cerebellar degeneration, polynévrite), connective tissue disorders (dermatomyositis, systemic lupus erythematosus), hematologic disorders (hemolytic anemia, disseminated intravascular coagulation), cutaneous disorders (acanthosis nigricans) and nephrotic syndrome, all with a poor prognosis [7,8]. Paraneoplastic erythroderma is rarely associated with ovarian cancer. Nevertheless, it can be the presenting sign of an ovarian neoplasm and should alert the clinician towards the possibility of internal malignancy.

The exact mechanism of occurrence of paraneoplastic erythroderma is not clear. It is thought to develop as a response to hormones or other active substances, like cytokines (interleukin 1, 2, 8) and cellular adhesion molecules (vascular cell adhesion molecule-1, intercellular adhesion molecule-1, E-selectin, P-selectin) released by cancer cells [9-11]. These substances induce skin infiltration with immune cells, resulting in a significant increase in the turnover rate of the epidermis, with consecutive erythema and scaling that affects more than 90% of the body surface and impairment of skin barrier function and thermoregulation [9-11]. Interestingly, ovarian carcinoma is known to represent one of the more immunogenic tumors [12].

For our patient, the parallel course of the ovarian carcinoma and cutaneous lesions firmly supports the diagnosis of paraneoplastic erythroderma, that proved a veritable cutaneous marker for the evolution of the internal neoplasia. Screening for underlying malignancy should be performed in all cases of erythroderma of unknown etiology.

CONCLUSIONS

Erythroderma is a rare manifestation of ovarian cancer. The parallel course of the ovarian carcinoma and cutaneous lesions in our patient firmly supports the diagnosis of paraneoplastic erythroderma, that proved a veritable cutaneous marker for the evolution of the internal neoplasia. Screening for underlying malignancy should be performed in all cases of erythroderma of unknown etiology.

REFERENCES