TOXIC EPIDERMAL NECROLYSIS IN A FEMALE WITH METASTATIC BREAST CANcer TREATED WITH VINorelbine

NÉCROLYSE ÉPIDERMIQUE TOXIQUE CHEZ UNE FEMME AVEC UN CANCER DU SEIN MÉTASTATIQUE TRAITÉE PAR VINORÉLINE

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SUMMARY. Vinorelbine is an anticancer agent with high clinical efficacy for the treatment of metastatic breast cancer. Toxic epidermal necrolysis is a rare but serious cutaneous adverse reaction associated with drug therapy. We hereby present a case report of a patient with metastatic breast cancer, treated with vinorelbine, who developed toxic epidermal necrolysis. To the best of our knowledge, ours is the second case report describing this exceptional dermatologic associated with vinorelbine. In June 2014, a 33-year-old female was treated for localized breast cancer. In December 2016, a brain magnetic resonance imaging revealed cerebral and cerebellar recurrence of the breast cancer. Whole brain radiation therapy was administered and treatment with vinorelbine was subsequently initiated. On day 3 of the first cycle of chemotherapy, she presented a general malaise and an itchy rash with conjunctivitis, oral ulcers and diffuse alopecia. The clinical diagnosis was toxic epidermal necrolysis due to vinorelbine. The patient was transferred to the burn unit. Treatment with intravenous steroids, topical steroids and desloratadine was initiated. She subsequently developed Staphylococcus aureus bacteremia and died of multi-organ failure. Toxic epidermal necrolysis is an extremely rare, acute hypersensitivity reaction involving the skin and mucous membranes. Features more suggestive of toxic epidermal necrolysis are acute onset and rapid worsening of painful lesions of the skin and mucous membranes. Specific treatment with active interventions should be practiced in the context of an international and multicentre clinical study in order to give sufficient power for such trials in this rare disease.

Keywords: toxic epidermal necrolysis, metastatic breast cancer, vinorelbine

RÉSUMÉ. La vinorelbine est un agent anticancéreux très efficace dans le cancer du sein métastatique. La nécrose épidémique toxique est un effet indésirable médicamenteux cutané rare mais grave. Nous présentons le cas d’une patiente avec un cancer du sein métastatique traité par vinorelbine, qui a développé une nécrose épidémique toxique. À notre connaissance, c’est le deuxième cas de la nécrose épidémique toxique due à la vinorelbine. En juin 2014, une femme de 33 ans a été traitée pour un cancer mammaire localisé. En décembre 2016, elle a présenté des métastases cérébrales et cérébelleuses. Une radiothérapie encéphalique a été administrée puis un traitement par vinorelbine a été initié. Au troisième jour du premier cycle de chimiothérapie, elle a présenté un malaise général et une éruption cutanée avec démangeaisons accompagnée de conjonctivite, d’ulcères buccaux et d’alopecie diffuse. Le diagnostic était en faveur de la nécrose épidémique toxique à la vinorelbine. La patiente a été transférée à l’unité de brûture et a reçu des stéroïdes intraveineux et locaux et la desloratadine. Elle a ensuite développé une bactériémie à Staphylococcus aureus et est décédée d’une défaillance multiviscérale. La nécrose épidémique toxique est une réaction d’hypersensibilité aiguë extrêmement rare touchant la peau et les muqueuses. Elle est évoquée devant l’apparition aiguë et l’aggravation rapide de lésions douloureuses de la peau et des muqueuses. Un traitement spécifique avec des interventions actives doit être recherché dans le cadre d’une étude internationale et multicentrique, afin de donner assez de puissance à de tels essais dans cette maladie rare.

Mots-clés: nécrose épidémique toxique, cancer du sein métastatique, vinorelbine

Introduction

Vinorelbine (VNR) is an anticancer agent, and its affinity for mitotic microtubules causes a high clinical efficacy for the treatment of metastatic breast cancer (MBC), together with a good tolerability at therapeutically effective doses. Toxic epidermal necrolysis (TEN) is a rare but serious cutaneous adverse reaction associated with drug therapy, defined as erythema and desquamation involving more than 30% of body surface area. We hereby present a case report of a patient with MBC, treated with VNR, who developed TEN. To the best of our knowledge, ours is the second case report describing this exceptional dermatologic emergency associated with VNR.

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Case presentation

In June 2014, a 33-year-old female was treated for invasive ductal carcinoma of her right breast. She underwent lumpectomy and sentinel node procedure. The pathological TNM stage was T2N0M0. The human epidermal growth factor receptor 2 (HER2) was positive and the estrogen receptors (ER) and progesterone receptors (PR) were negative. The patient received adjuvant radiotherapy to the breast (50 Gy/25 fractions/5 weeks) and chemotherapy with doxorubicin and cyclophosphamide every 3 weeks for four cycles, followed by docetaxel every 3 weeks for four doses, and trastuzumab, beginning with the first dose of docetaxel and continuing for 1 year. Fifteen months after finishing trastuzumab, in December 2016, she consulted for increasing headache, gait disturbance and vomiting. A brain magnetic resonance imaging (MRI) revealed cerebral and cerebellar recurrence of the breast cancer. Whole brain radiation therapy (WBRT) (30 Gy/10 fractions/2 weeks) was administered. Clinical symptoms decreased quickly with an acceptable toxicity. Treatment with trastuzumab (8 mg/kg loading dose, then 6 mg/kg every 3 weeks) and VNR (25 mg/m2 on days 1 and 8 every 3 weeks) was subsequently initiated.

On day 3 of the first cycle of chemotherapy, she presented to the emergency department with a general malaise and an itchy rash, starting in the face but which soon involved her trunk, abdomen, neck, and bilateral upper and lower extremities (Fig. 1). Furthermore, conjunctivitis, oral ulcers and diffuse alopecia developed (Fig. 2). Dermatologic findings included erythematous and purpuric macules with flaccid bullae. Mild skin detachment and oozing of serous fluid were also concomitant (Fig. 3). As the most recently introduced drug was VNR, and since the rash involved more than 30% of the body surface area, the clinical diagnosis was TEN due to VNR. The patient was transferred to the burn unit. Treatment with intravenous steroids (120 mg methylprednisolone daily), topical steroids and desloratadine was initiated. She subsequently developed Staphylococcus aureus bacteremia. Despite treatment with piperacillin/tazobactam, the patient’s condition deteriorated with a fever of 39 °C, and she died of multi-organ failure.

Discussion

In 1956, Alan Lyell, a Scottish dermatologist, reported the first case of TEN.³⁶ TEN is an extremely rare, acute hypersensitivity reaction involving the skin and mucous membranes. Its incidence is approximately 0.4-1.2 cases per million person-years. Medications are responsible for at least 70% of cases of TEN. Allopurinol, antiepileptics (carbamazepine, lamotrigine, phenobarbital, phenytoin), nevirapine, oxicam NSAIDs and antibacterial sulfonamides are the most common drugs causing TEN.⁷⁻⁸ In the literature, only a single case of localized epidermal necrolysis after intravenous injection of VNR has been reported by Misery et al.⁴

Several genetic factors influence the risk of developing TEN. In Asian populations, an important association was established between the human leucocyte antigen (HLA) genotype and Stevens-Johnson syndrome (SJS)/TEN induced by carbamazepine (HLA B*1502) and allopurinol (HLA B*5801).⁵⁻⁶

TEN usually presents with a prodrome of fever, malaise and upper respiratory tract symptoms 7–21 days after the initiation of the causative drug. Features more suggestive of TEN are acute onset and rapid worsening of painful lesions of the skin and mucous membranes, including eyes, mouth, nose and genitalia. Skin lesions manifest as blisters and ulcerations arising on generalized macules with purpuric centers. The large denuded areas lead to massive loss of fluid and protein, bleed-
The present case serves to alert clinicians to this rare but serious side effect of a commonly prescribed anticancer agent. Early diagnosis of TEN and multidisciplinary supportive care may improve prognosis. Specific treatment with active interventions should be practiced in the context of an international and multicentre clinical study in order to give sufficient power to such trials in this rare disease.

**Table 1 - SCORTEN (Score of toxic epidermal necrosis)**

<table>
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<tr>
<th>Number of parameters</th>
<th>Predicted mortality</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>1</td>
<td>4%</td>
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<td>12%</td>
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<td>6</td>
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<tr>
<td>7</td>
<td>99%</td>
</tr>
</tbody>
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Parameters: age ≥40 years; malignancy; heart rate <120 beats/min; epidermal detachment >10% of body surface area; serum urea >10 mmol/L; serum glucose >14 mmol/L; serum bicarbonate <20 mmol/L.

**BIBLIOGRAPHY**