

## CASE REPORT

# Bullous pemphigoid, malignant acanthosis nigricans, and erysipeloid carcinoma in a woman with gastric adenocarcinoma

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## Key Clinical Message

Bullous pemphigoid did not follow the course of Gastric Carcinoma relapse and remission, unlike the malignant acanthosis nigricans which was in alignment with the paraneoplastic effect of the Gastric Carcinoma.

## Abstract

Acanthosis nigricans (AN) is a dermatosis characterized by the presence of hyperpigmented, velvety cutaneous thickening in the flexural areas, posterior neck, and occasionally the extensor surfaces of hand, face, and oral mucosa. AN is commonly associated with insulin resistance, drugs, and rarely internal malignancy (malignant AN). Bullous pemphigoid (BP) is an autoimmune blistering disease characterized by tense blisters involving the skin of mainly elderly patients. The association of BP and malignancy is not well established and the co-existence of BP with AN has not been reported. Here we report a 58-year-old, event-free gastric adenocarcinoma with three types of skin findings with different pathogenesis—BP, malignant AN, and erysipelas-like metastasis.

## KEYWORDS

bullous pemphigoid, erysipeloid carcinoma, gastric adenocarcinoma, malignant acanthosis nigricans

## 1 | INTRODUCTION

Bullous pemphigoid (BP) is an autoimmune sub-epidermal blistering disorder of the skin. Its association with malignancy is debatable, but several cases of BP have been reported in association with internal malignancies. Malignant acanthosis nigricans is a paraneoplastic syndrome associated with advanced cancer and gastric adenocarcinoma is the most common reported malignancy with acanthosis nigricans. Here,

we report a 58-year-old female known case of event-free gastric showing three types of skin findings with different pathogenesis—BP, malignant AN, and erysipelas-like metastasis.

## 2 | CASE REPORT

A 58-year-old female known case of previously treated gastric adenocarcinoma and considered event-free by her

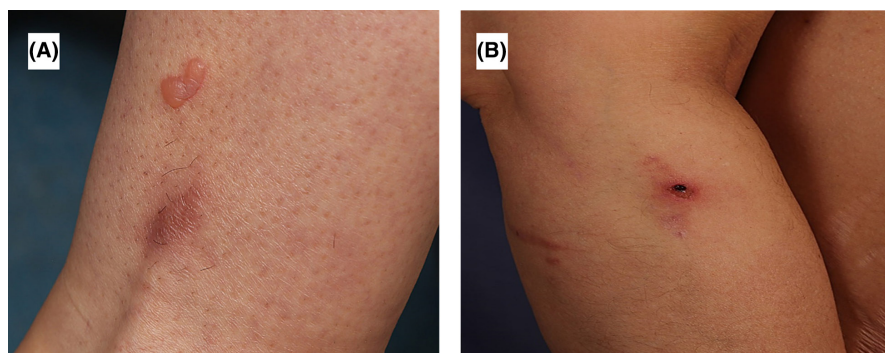
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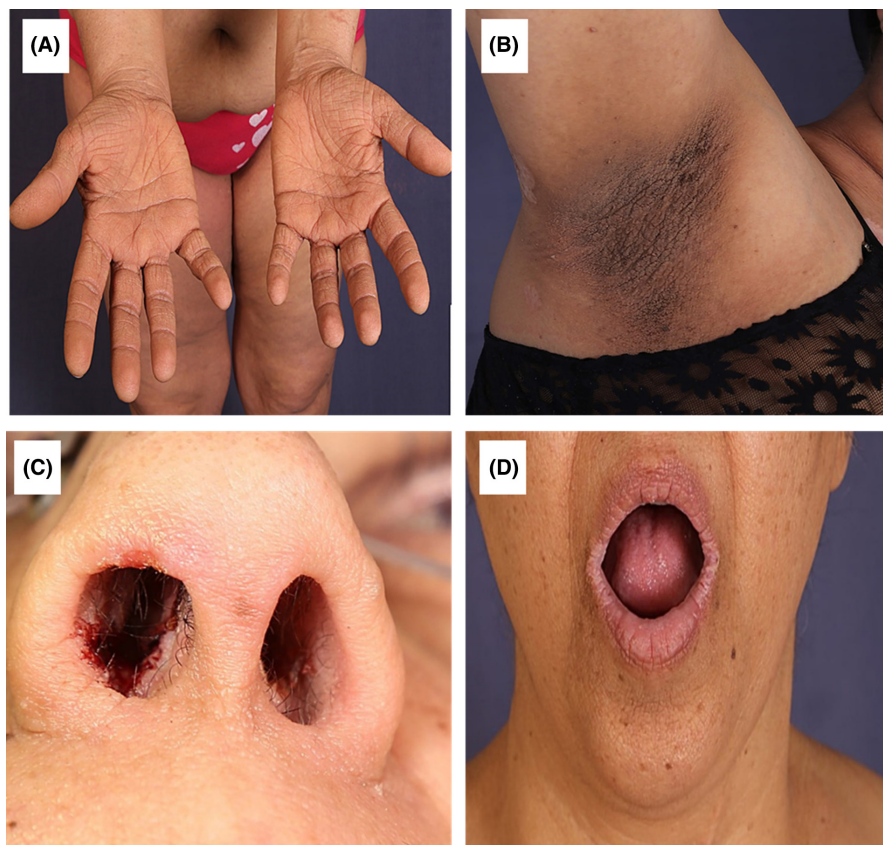
oncologist, presented to Razi Dermatology Hospital with a 1-month history of urticarial plaques and tense blisters on trunk and extremities in August 2019. Biopsy of the skin lesions revealed a sub-epidermal blister, filled with eosinophils with marked eosinophilic dermal infiltration. Direct immunofluorescence (DIF) showed linear IgG and C3 along the basement membrane zone. ELISA results for BP 180 and 230 were 30 and 20 IU/mL, respectively. Lack of mucosal bullous or erosive lesions was against the diagnosis of paraneoplastic pemphigus and mucous membrane pemphigoid and she was diagnosed with BP. Topical clobetasol ointment (45 g/day) and systemic prednisolone (up to 30 mg/day) were not effective at controlling the skin lesions. Intravenous rituximab (500 mg weekly for 4 weeks) was added to her regimen. She went into partial remission within 1 month after rituximab.

Her occasional tense blisters were controlled by topical clobetasol (Figure 1A,B). On subsequent follow-up visits for her blistering disease during the next months, progressive, hyperpigmented, velvety thickening of the neck, axilla, groins, palms, soles, nose, and lip, in addition to oral mucosal thickening was noted (Figure 2A–D on December 2020).

The clinical findings which were in favor of malignant AN prompted evaluation for the recurrence of her previous malignancy. Evaluation by abdominal ultrasound showed multiple hepatic metastases. A new chemotherapeutic course was initiated by her oncologist which led to the gradual resolution of her AN. Interestingly, there were only occasional mild relapses of her BP with no temporal relation to the status of the underlying malignancy. Lastly, in September 2021, she presented with a large, extremely



**FIGURE 1** Bullous pemphigoid: Occasional bullae in the lower leg, (A) intact bullae, (B) hemorrhagic lesion. (August 2019).



**FIGURE 2** Malignant acanthosis nigricans: (A) Tripe palm, (B) Hyperpigmented, velvety thickening of the axilla, (C) Nasal mucosal thickening, and (D) Oral mucosal thickening. (December 2020).



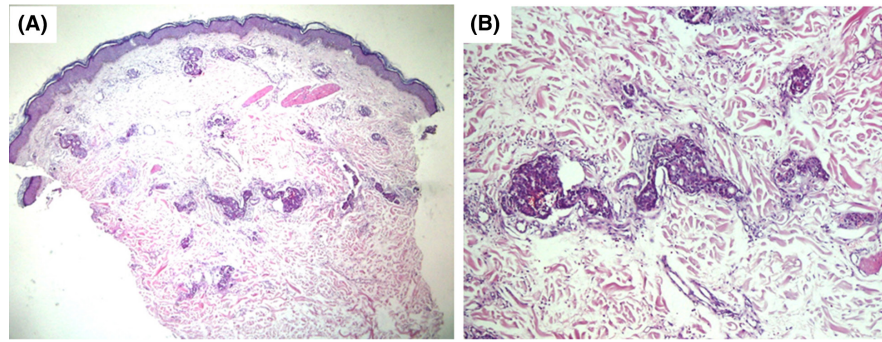
**FIGURE 3** Skin metastasis: Erysipelas-like plaque on the right upper thigh as a result of direct infiltration of the skin by malignant cells (September 2021).

painful, tender, erysipelas-like plaque on her right thigh which was unresponsive to systemic intravenous antibiotics (Figure 3). In the meantime, a gradual recurrence of the AN lesions was also noted. A deep biopsy of the thigh lesion showed intravascular metastatic adenocarcinoma (Figure 4A–C). Unfortunately, she died in 2022 from complications related to metastatic gastric adenocarcinoma.

### 3 | DISCUSSION

Gastric cancer is the fifth most common neoplasm and the third most deadly cancer with an estimated 783,000 deaths

in 2018.<sup>1</sup> Although cutaneous signs of internal malignancies are rare dermatologists may play a great role in early diagnosis when cutaneous signs are the sole manifestations of an asymptomatic patient. The cutaneous signs of internal malignancies are protean; including pigmented papillomatous plaque in gastric adenocarcinoma, palmo-plantar thickening in hepatic metastasis, acral erythematous psoriasiform plaques in squamous cell carcinoma of the esophagus, and erysipelas-like plaque in gastric cancer.<sup>2</sup> Cutaneous signs related to gastric adenocarcinoma either precede the diagnosis of the malignancy or follow it or may take a course indicative of remission or recurrence of the malignancy. Our patient showed two forms of skin manifestations of gastric adenocarcinoma, that is, direct infiltration of the skin by the metastatic cells as in the erysipelas-like plaque of the thigh and the paraneoplastic effect of the advanced gastric cancer in causing hyperpigmented plaques in the flexural surfaces, as malignant AN. She also had BP, a condition with a disputable association with malignancy. While the association of malignant AN with gastric adenocarcinoma is well established, the association of BP with internal malignancy is debatable and probably related to the older age of the patient. The English national record linkage study found no increased risk for concurrent or subsequent malignancies in BP patients.<sup>3</sup> In a cohort study, Sophie et al reported no association between BP and malignancy.<sup>4</sup> Meanwhile, there are a few case reports describing a possible association with internal malignancies and BP. Tanaka et al reported a 54-year-old female with transitional cell carcinoma of the bladder and BP.<sup>5</sup> They postulated the presence of a possible circulating factor reactive against both the skin basement membrane zone and bladder carcinoma. Joycelin et al. reported squamous cell carcinoma (SCC) of the tongue in a patient with recalcitrant BP, the recalcitrant BP was remitted after surgical excision of the SCC.<sup>6</sup> A meta-analysis concluded that the overall event rate of malignancy was higher for the pemphigoid group than in matched control.<sup>7</sup> In our case, BP developed when the patient was considered event-free for her adenocarcinoma, she achieved clinical remission of her BP after receiving rituximab (2 gm) plus topical and low dose corticosteroids. She experienced only minor relapses of her BP not temporally related to her malignant AN and skin metastasis. Overall, we can hypothesize that the course of BP was not affected by the course of the gastric adenocarcinoma; although, a drawback of this conclusion is the prolonged effect of rituximab injection on causing remission of BP. Considering its response to rituximab and prednisolone, a paraneoplastic nature of BP is unlikely in this case. Meanwhile, malignant AN was of a true paraneoplastic disease with nearly complete resolution after chemotherapy of the adenocarcinoma and



**FIGURE 4** Metastatic adenocarcinoma: Epithelial neoplasm in the dermis composed of nests and aggregates of atypical cells with glandular architecture, focal necrosis, and increased mitotic activity with marked dermal vessel involvement; unremarkable epidermis. (Hematoxylin and Eosin stain, (A) 4x; (B) 20x).

slow reappearance just before she developed erysipelas-like plaque of the right thigh. Malignant AN occurs in elderly patients with a rapidly, progressive velvety thickening of the flexural skin surfaces and oral mucosa unlike the younger, slowly occurring benign AN but patients as young as 30 years old with malignant AN has been reported.<sup>8</sup> Malignant AN has a well-established association with internal malignancies, especially gastric adenocarcinoma, but an association with clear cell lung carcinoma,<sup>9</sup> bladder carcinoma,<sup>10</sup> pancreatic, ovary, esophageal, and renal cell carcinoma have also been reported.<sup>11</sup> The coexistence of AN and BP had been rarely described. Ives and Gold reported AN and BP in a patient with metastatic carcinoma of the cervix.<sup>12</sup> The pathophysiology of malignant AN is postulated to be mediated through increased transformed growth factor (TGF), which acts on the epidermal growth factor receptor in the epidermis.<sup>13</sup> BP is an autoimmune-mediated dermatosis of the dermo-epidermal junction and a causal link between BP and malignant AN cannot be established. Finally, erysipeloid carcinoma is an unusual manifestation of internal malignancy and occurs due to direct infiltration of the skin by malignant cells. It indicates distant metastasis and poor prognosis. Erysipeloid carcinoma has been reported mainly in breast carcinoma but very rarely in gastric adenocarcinoma. In rare instances, it may be the initial presentation of gastric carcinoma.<sup>14</sup>

## 4 | CONCLUSION

The clinical findings in this patient were interesting from different aspects: first of all, the association of BP with cancer is not well established, and in this patient, the natural course of BP did not follow the course of the underlying adenocarcinoma. On the other hand, when it comes to malignant AN and tripe palm, the paraneoplastic nature of this entity (appearance of lesions concurrent

with multiple liver metastases and clearing of lesions after chemotherapy) is well-shown. At last, skin metastasis masquerading cellulitis, erysipelas, or to a lesser degree, BP, Wells syndrome, panniculitis, and lymphoma, was only rarely reported. The intravascular histopathology of the metastatic lesion is noteworthy.

## AUTHOR CONTRIBUTIONS

**Saman Al-Zahawi:** Writing – original draft; writing – review and editing. **Yasaman Sadeghi:** Writing – review and editing. **Vahidesadat Azhari:** Supervision; visualization. **Hamidreza Mahmoudi:** Conceptualization; supervision. **Maryam Daneshpazhooh:** Conceptualization; supervision; writing – review and editing.

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None.

## CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

## DATA AVAILABILITY STATEMENT

The authors elect not to share data.

## CONSENT

Written informed consent was obtained from the patient before she passed away to publish this report in accordance with the journal's patient consent policy".

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