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CASE REPORT

Sequential occurrence of primary cutaneous indeterminate cell histiocytosis after oesophageal cancer and subsequent bullous pemphigoid: a case report

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Abstract

Aims/Background Indeterminate cell histiocytosis is a rare proliferative histiocytic disease with an unknown aetiology, which shares immunophenotypic features of both Langerhans cells and macrophages. There is a relationship between indeterminate cell histiocytosis and cancer, while there are no reports about indeterminate cell histiocytosis and bullous pemphigoid. In this study, we reported the rare case of a patient with primary cutaneous indeterminate cell histiocytosis who had been diagnosed with oesophagal cancer and later developed bullous pemphigoid. The objective of this clinical case report is to analyse the association between solid tumours and indeterminate cell histiocytosis and focus on the coexistence of indeterminate cell histiocytosis and bullous pemphigoid in a patient with cancer.

Case Presentation This study presented the case of a 75-year-old man who exhibited annular erythema lesions of variable size and papules scattered over his chest, abdomen, and limbs, along with four bullae on his thigh, persisting for 1.5 months. The patient also had a 9-month history of oesophageal cancer treated with radical radiotherapy. Histopathology and immunohistochemistry confirmed cutaneous indeterminate cell histiocytosis. Bullae and blisters developed on the lower limbs 38 days after treatment. A diagnosis of bullous pemphigoid was established based on clinical and histopathological features and results of direct immunofluorescence and enzyme-linked immunosorbent assay.

Results Histopathological examination of the abdominal lesion revealed an accumulation of mononuclear cells in the dermis, with infiltration of eosinophils and lymphocytes in the superficial dermal layer. The histology of the blister on the thigh indicated the formation of an old subepidermal blister, with slurry and eosinophils present within the blister, and infiltration of eosinophils, lymphocytes, as well as histiocytoid cells in the superficial dermal layer. Immunohistochemical staining was positive for CD1a, S100, and CD68, and negative for CD207. Histopathological examination of blisters and bullae on the lower limbs revealed a subepidermal blister with infiltration of a large number of eosinophils within the blister and the dermis beneath it. Direct immunofluorescence showed that immunoglobulin Gs (IgGs) were linearly deposited in the basal membrane zone.

Conclusion The coexistence of oesophageal carcinoma, indeterminate cell histiocytosis, and bullous pemphigoid in a single patient represents a rare case that warrants consideration of possible underlying mechanisms.

Key words: Bullous pemphigoid; Cancer; Case report; Indeterminate cell histiocytosis

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Introduction

Indeterminate cell histiocytosis (ICH) is a rare proliferative histiocytic disease, first described by Wood et al (1985). It predominantly affects adults and has no gender predilection. The pathogenesis of ICH remains unknown, and it can present as solitary or multiple papules and/or nodules, which typically have a benign course (Zanella et al, 2023). In addition to primarily involving the skin, ICH may manifest extra-cutaneously in the mucosa, cornea, conjunctiva, and visceral organs. However, these occurrences are very rare. Diagnosis of

ICH is based on clinical features, immunophenotype, and histopathology. The current understanding of ICH is limited to case reports and small series.

There is an association between ICH and cancer, particularly haematopoietic malignancies and follicular lymphoma (Davick et al, 2018). However, coexistence with a solid tumour and a paraneoplastic-like evolution has also been reported (Pallure et al, 2014). Bullous pemphigoid (BP) is a subepidermal blistering skin disease characterised by the presence of autoantibodies to hemidesmosomal plaque protein BPAg1 and transmembrane protein BPAg2. The relationship between BP and cancer is controversial. Before the present study, the coexistence of ICH and BP had not been previously reported.

In this study, we reported a case of cutaneous ICH following oesophageal carcinoma and subsequently complicated by BP. A comprehensive literature review analysing the possible causes of the case was presented.

Case report

Patient baseline data

A 75-year-old man presented with a 1.5-month history of scattered annular erythema and papules and itching on his chest, abdomen, and limbs (**Figures 1A, B**). The lesions, varying in size, progressively increased in number and did not resolve over time. Additionally, four bullae were observed on the patient's thigh (**Figures 1C, D**). Histopathological (**Figure 2**) and immunohistochemical (**Figure 3**) examinations were performed. 38 days later, the patient returned to our dermatology clinic with blisters and bullae on the lower limbs (**Figure 4A**). Histopathological examination (**Figure 4B**), direct immunofluorescence (DIF) (**Figure 4C**), and enzyme-linked immunosorbent assay (ELISA) were performed. Nine months before

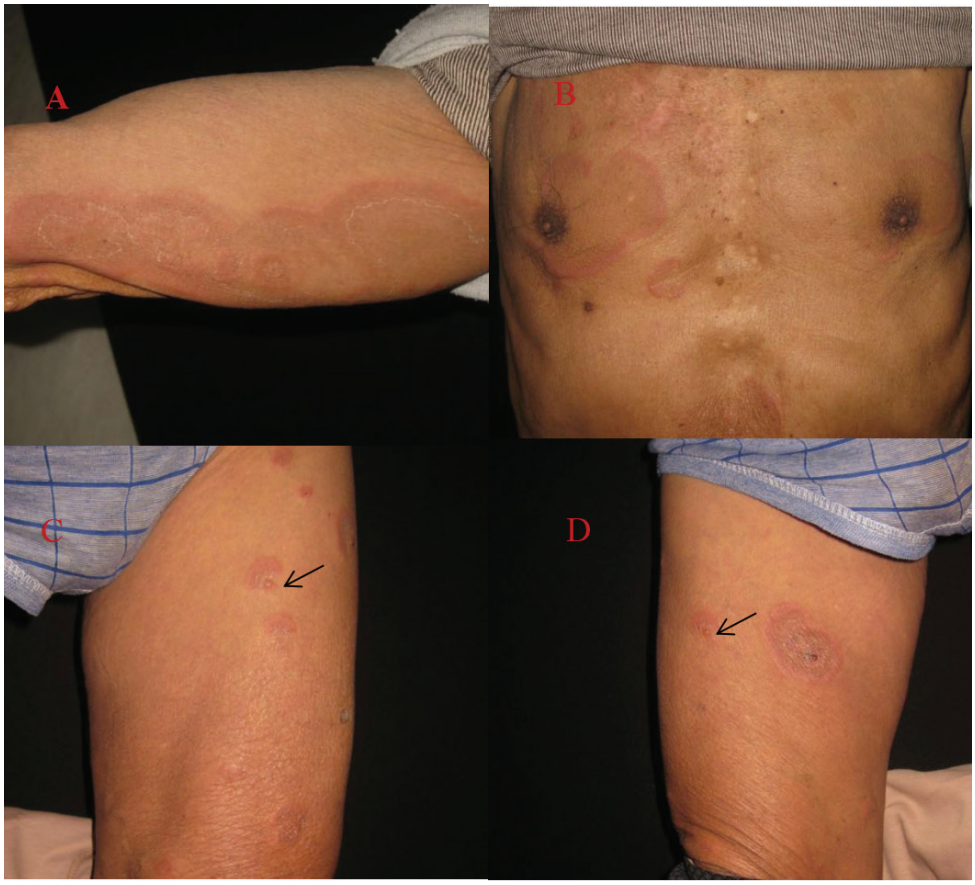

Figure 1. Annular erythema and papules on the patient's chest (B), abdomen (B), limbs (A, C, D), and a bulla (the arrow) on the thigh.

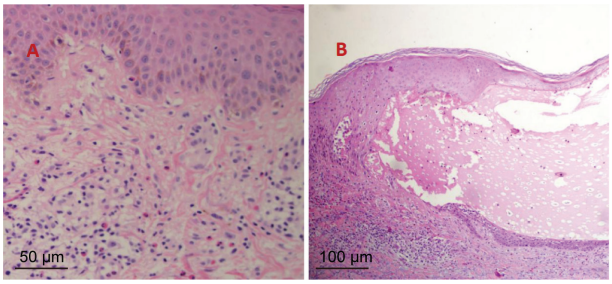

Figure 2. Histology of the skin biopsy. (A) The abdominal lesion, histopathological examination showed accumulation of mononuclear cells in the dermis, with infiltration of eosinophils and lymphocytes in the superficial dermal layer (scale bar=50 μm) (HE staining, 400×); (B) The thigh lesion, histology indicated the formation of an old subepidermal blister, with slurry and eosinophils present within the blister and infiltration of eosinophils, lymphocytes, and histiocytoid cells in the superficial dermal layer (scale bar=100 μm) (HE staining, 200×). HE, haematoxylin and eosin.

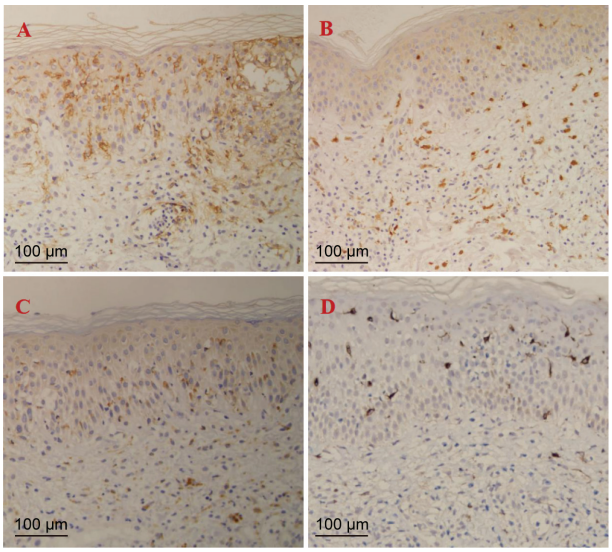

Figure 3. Immunohistochemical findings of the patient (scale bar=100 μm) (200×). (A) CD1a: strongly positive in the epidermis and dermis; (B) S100: positive in the epidermis and dermis; (C) CD68: positive in the epidermis and dermis; (D) CD207(Langerin): negative in the dermis.

presenting at our department, the patient had been diagnosed with oesophageal cancer at another hospital and treated with radical radiotherapy, which had since been completed. There was no history of similar conditions in the patient's family.

Research methods

Skin specimens were taken from the abdominal lesion and thigh blister for haematoxylin and eosin (HE) staining and immunohistochemical stains, and from a bulla of the lower limb for haematoxylin and eosin (HE) staining. The DIF specimen was obtained from the normal skin surrounding the bulla. The specimens were fixed in 4% paraformaldehyde (30525-89-4, Baoding LingYe Trade Co., Ltd., Baoding, Hebei, China), embedded in an automatic paraffin embedding machine (EG1150, LEICA Inc., Wetzlar, Germany) to make tissue wax blocks, and then cut into sections with a thickness of 4 μm using a pathological microtome (HM325, Microm Internation GmbH., Walldorf, Germany). Two complete specimens were selected and mounted on a poly-L-lysine treated slide (01-11215-50, Hangzhou Heaven Biotechnology Science Co., Ltd., Hangzhou, China) for HE staining and immunohistochemical stains. HE staining, immunohistochemical stains, and DIF were performed on a platform from the pathology department of Zhejiang Provincial Hospital of Dermatology using standard methodologies. The serological detection of

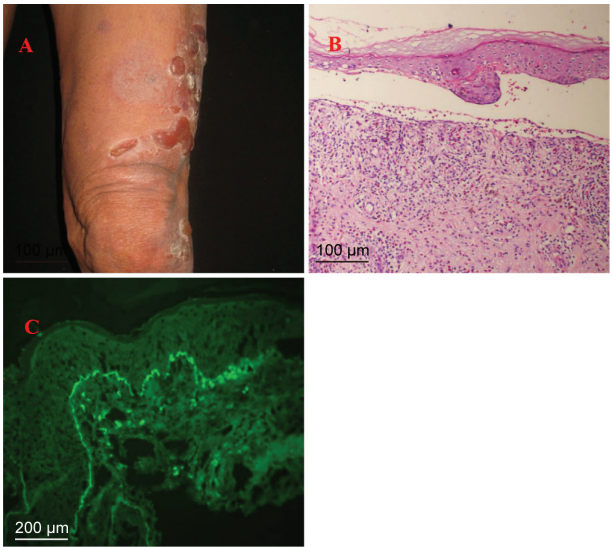

Figure 4. Clinical findings of bullous pemphigoid on the lower limbs. (A) Clinical photograph of bullous pemphigoid on the lower limbs; (B) Histopathologic examination showed the subepidermal blister (scale bar=100 μm) (HE, 200×); (C) Direct immunofluorescent showed immunoglobulin Gs (IgGs) linearly deposited in the basal membrane zone (scale bar=200 μm) (100×).

antibodies against bullous skin with the method of ELISA was performed on platform form Zhejiang Dean Diagnostic Technology Co., Ltd., using standard methodology. CD3 (ZA-0503), CD4 (ZM-0418), CD8 (ZA-0508), CD45RO (ZM-0055), CD5 (ZM-0280), CD7 (ZA-0589), CD20 (ZA-0293), CD79a (ZA-0293), CD1a (ZA-0544), S-100 (ZA-0225), CD68 (ZM-0060), CD207/Langerin (ZM-0385), CD56 (ZM-0057), Ki-67 (ZM-0166) antibodies (Beijing Zhongshan Jinqiao Biotechnology Co., Ltd., Beijing, China) were used in immunohistochemistry. Antibodies including immunoglobulin G (IgG) (ZF-0306), IgA (ZF-0305), IgM (ZF-0307) (Beijing Zhongshan Jinqiao Biotechnology Co., Ltd., Beijing, China) and C3 (sc-28294) (Santa Cruz Biotechnology, Santa Cruz, CA, USA) were used in DIF, and BP180 (7695CN), BP230 (7613E), Dsg 1 (7880CN), and Dsg 3 (7885CN) (MBL, Tokyo, Japan) were used in ELISA.

Treatment methods

Based on the diagnosis of ICH, the patient received symptomatic treatment, including intravenous Glycyrrhizin, oral antihistamine (Medaclloratadine), topical Halometasone cream, and a humectant, in the Department of Dermatology. The patient was discharged with a slight improvement in his condition after a week. After being diagnosed with BP, the patient was advised to undergo corticosteroid treatment for BP and was informed about possible side effects. However, the patient did not adhere to the recommended treatment regimen. A telephone follow-up revealed that the patient died of multiple organ failure approximately 8 months later.

Result

Histopathological examination of the abdominal lesion revealed an accumulation of mononuclear cells in the dermis, with infiltration of eosinophils and lymphocytes in the superficial dermal layer (Figure 2A). The histology of the blister on the thigh indicated the formation of an old subepidermal blister, with slurry and eosinophils present within the blister and infiltration of eosinophils, lymphocytes, and histiocytoid cells in the superficial dermal layer (Figure 2B). Immunohistochemical staining (Figure 3) was positive for CD1a, S100, and CD68, and negative for CD207. Based on these findings, a diagnosis of ICH was made. Further medical tests, including routine laboratory tests, a bone marrow biopsy and a computed tomographic (CT) scan, did not indicate any abnormalities in other systems. Histopathological examination of blisters and bullae on the lower limbs revealed

a subepidermal blister with infiltration of a large number of eosinophils within the blister and the dermis beneath it, as seen in Figure 4B. Direct immunofluorescence showed immunoglobulin Gs (IgGs) linearly deposited in the basal membrane zone (Figure 4C). Based on these features, a diagnosis of BP was made.

Discussion

Indeterminate cell histiocytosis exhibits immunophenotypic features of both Langerhans cells and non-Langerhans cells, characterised by positive expression of CD1a, S-100, and CD68 while being negative for CD207/Langerin in the dermis. CD207/Langerin is associated with the formation of Birbeck granules and is considered a marker for Langerhans cells. Therefore, based on our study findings, a diagnosis of ICH was made rather than Langerhans cell histiocytosis (LCH).

Morphologically, ICH closely resembles LCH. A previous study reported associations between LCH and tumours (Ma et al, 2019). Bubolz et al (2014) reported an average *BRAFV600E* oncogene mutation rate of 48.5% in LCH cases, and Badalian-Very et al (2010) identified recurrent *BRAFV600E* gene mutations in LCH. The *BRAFV600E* mutation has also been detected in two out of seven ICH cases (Kinoshita et al, 2021). The *BRAF* gene is well-established as an oncogene implicated in various cancers including colorectal cancer, liver cancer, pancreatic cancer, malignant melanoma, and papillary thyroid carcinoma, playing a pivotal role in tumorigenesis, development, and metastasis (Hussen et al, 2021; Penning et al, 2021; Chen et al, 2023). Therefore, the presence of the *BRAFV600E* mutation may explain the occurrence of ICH following oesophageal cancer in our case. Additionally, besides the *BRAFV600E* mutation, *ETV3-NCOA2* translocation has been identified in some ICH cases (Belina et al, 2022).

Bullous pemphigoid is an autoimmune blistering disorder primarily affecting elderly men. However, the relationship between BP and cancer remains controversial. While some reports suggest that malignancy can occur before, during, or after the appearance of typical bullous skin lesions, the precise pathogenetic mechanism underlying this correlation remains unclear (Asdourian et al, 2022). Nevertheless, several studies have convincingly demonstrated no significant association between BP and tumours (Chen et al, 2019; Shen et al, 2022).

In our case, the patient had received radiation therapy (RT) for oesophageal carcinoma. A potential association between RT and the development of BP has been suggested. Many case reports or small case series of RT-associated BP have been documented. Nguyen et al (2014) described 29 patients with RT-associated BP based on existing literature and observed that patients with breast, lung, vulvar, and oesophageal cancers developed BP following RT, with 27 out of 29 (93%) initially presenting with localised BP. Clinically, many of these case reports or small case series demonstrated localised BP following RT at the radiated location, with rare reports of patients with BP at non-irradiated sites or developing generalised BP (Ashack et al, 2020). However, the bullae of the patient in our case mainly appeared on the lower limbs. There seemed to be little correlation between RT and BP in our case. Interestingly, a case of oesophageal cancer that developed BP localised to non-irradiated sites has been reported (Nguyen et al, 2014). To date, the pathogenesis of developing BP following RT is unknown. Various hypotheses regarding the potential mechanisms underlying RT-associated BP have been proposed. These include the release of antigens following RT-induced apoptosis of tumour and epidermal cells, altered keratinocyte surface antigenicity due to radiation, the induction of a radiation-sensitive population of T-suppressor cells that can interfere with immune surveillance, and altered levels of both matrix metallopeptidase-9 (MMP-9) and growth factors such as vascular endothelial growth factor receptor (VEGFR), which have been implicated in the pathogenesis of BP (Ashack et al, 2020).

Interestingly, ICH and BP occurred together in our case, which had not been reported before. However, Akdogan et al (2020) presented a case of multi-lesional cutaneous ICH in a 27-year-old male patient with systemic lupus erythematosus together with antiphospholipid antibody syndrome (APS), both of which are autoimmune disorders. Furthermore, many studies have reported associations between BP and various autoimmune diseases, suggesting

that they could share a pathogenetic mechanism (Moro et al, 2020). Therefore, it is worth considering whether there is also a link between ICH and autoimmune disorders.

Conclusion

In this particular case, the simultaneous occurrence of oesophageal carcinoma, ICH, and BP in a single patient raises important questions regarding potential associations among them. This highlights the need for further investigation elucidate the possible mechanisms linking cancer with the development of ICH and BP.

Learning points

- Indeterminate cell histiocytosis is a rare proliferative histiocytic disease diagnosed by histopathological and immunohistochemical examinations.
- There is an association, although uncommon, between ICH and solid cancer.
- Bullous pemphigoid is an autoimmune, subepidermal blistering disease characterised by tense bullae on erythematous or normal skin.
- Diagnosis is dependent on Histopathological examination, DIF and ELISA.
- Radiation therapy may explain the coexistence of BP and cancer.

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Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Author contributions

Programme administration: XXJ and DL. Conceptualisation: XXJ. Data curation: XXJ, LLS, DL and LZ. Methodology: XXJ, LLS and DL. Investigation: XXJ and LLS. Writing-original: XXJ and DL. Writing-review editing: all authors. Resources: XXJ, LLS and LZ. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate

The study was approved by the ethics committee of Zhejiang Provincial Hospital of Dermatology (approval No.202403k). All participants signed an informed consent form.

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Conflict of interest

The authors declare that they have no competing interests.

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