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Case Report

Reactive Angioendotheliomatosis Secondary to Perforated Peptic Ulcer Surgery in a Patient with Coronary Artery Disease

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Reactive angioendotheliomatosis (RAE) is a rare disease characterized by angioproliferation limited to skin. Patients with coexistent systemic diseases are most vulnerable. Histopathologically, it is marked by hyperplasia of endothelial cells with vascular proliferation but without cytological atypia. Although the pathogenesis is still not completely understood, it has been proposed that immunologic factors and hypoxic stimulus lead to RAE. In what is the first reported case in Taiwan, we describe a 76-year-old female with a history of coronary artery disease who developed RAE after perforated peptic ulcer surgery.

Keywords: Reactive angioendotheliomatosis, RAE, surgery

Introduction

Reactive angioendotheliomatosis (RAE) is a rare benign angioproliferative condition of the skin, which mainly arises in patients with underlying systemic diseases or inflammatory conditions.[1] RAE usually presents solely in the skin and generally resolves or improves spontaneously after the cessation of occlusion and hypoxia.[2] The histological hallmark of RAE is intravascular hyperplasia of endothelial cells with vascular proliferation in the dermis and subcutis. Based on histologic findings of benign vascular proliferation, the presentation of RAE is similar to that of glomeruloid angioendotheliomatosis, angiopericytomatosis, diffuse dermal angiomatosis, and acroangiodermatitis. It is crucial to differentiate RAE from malignant tumors such as Kaposi's sarcoma and angiosarcoma. Herein, we report the first case of RAE after perforated peptic ulcer surgery in Taiwan.

Case presentation

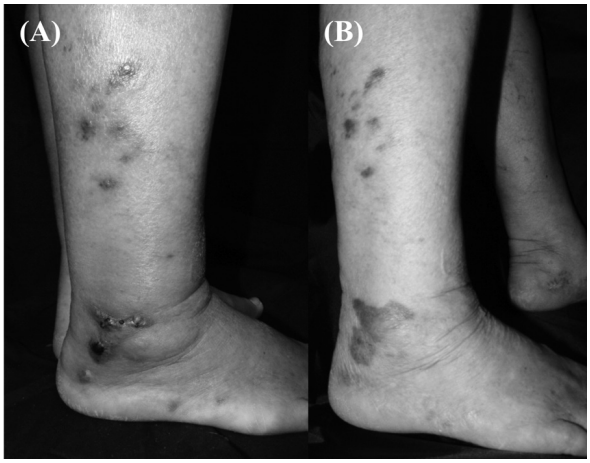

Figure. 1 (A) Multiple non-tender violaceous nodules and papuloplaques, some with central ulcer and blackish crust; (B) After 6 months no new lesions developed, but hyperpigmentation remained.

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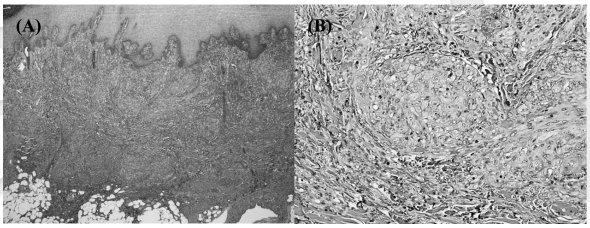

Figure. 2 (A) Multinodular vascular proliferation in the dermis and superficial subcutis (hematoxyline and eosin, H&E, x40); (B) Epithelioid epithelium proliferation without endothelial atypia (hematoxyline and eosin, H&E, x200)

A 76-year-old woman with a history of coronary artery disease for which she had been taking regular medication presented with multiple bluish to violaceous papules and nodules on the bilateral lower legs and insteps (Figure 1A), which progressed rapidly two weeks after surgery for a perforated peptic ulcer.

The surgery was performed due to the sudden onset of epigastric pain. Computed tomography showed hollow organ perforation with peritonitis, which was treated with simple closure with omental patch. After the operation, she was fitted with an endotracheal tube with ventilator support due to respiratory dysfunction and pneumonia. Culture of the pus from the abdominal wound revealed *Staphylococcus aureus* infection.

On the 12th postoperative day, ecchymosis and crust formation on the bilateral lower legs were noted. Physical examination showed multiple non-tender violaceous nodules and papuloplaques. Some of the lesions had merged, while others had developed central ulceration and blackish crust. The patient denied any cancer history, use of immunomodulatory medication, trauma history, or body weight loss, as well as any systemic disease except for coronary artery disease. Non-contributory family history was also noted.

Laboratory examination results included normal values for ANCA, cryoglobulin, and antibody levels of HBV and HCV. Coagulation factor survey and autoimmune test were likewise unremarkable.

We performed a skin biopsy on a solitary violaceous papule on her left inner ankle. Hematoxylin and eosin stain revealed multilobular vascular proliferation with intraluminal endothelial proliferation in the dermis and superficial subcutis without endothelial

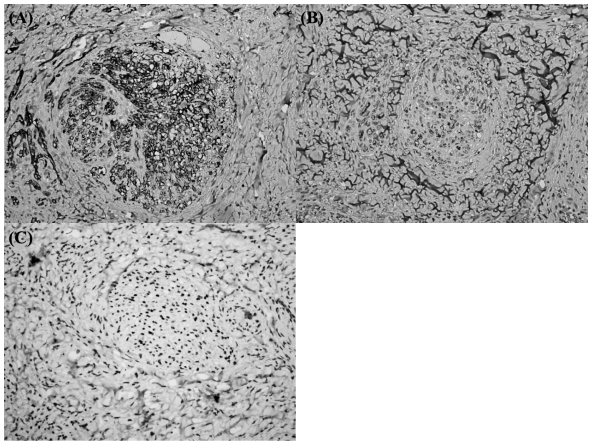

Figure. 3 Immunochemistry: (A) CD31 staining; (B) focal CD34 staining; (C) HHV-8 staining

atypia. Mild inflammatory cell infiltration was present (Figure 2A). There were no features of Kaposi's sarcoma, such as eosinophilic spindle cell proliferation, slit-like blood vessels, chronic inflammatory cell infiltration involving plasma cells, or promontory sign(s) with jagged vascular space surrounding adnexa. Immunohistologically, the intraluminal proliferative endothelial cells stained with anti-CD31 (Figure 3A) were within pre-existing blood vessels. Occasional mitotic activity and extravasations of red blood cells were noted. Moreover, there was positive HHV-8 staining (Figure 3C) but only focal CD34 staining (Figure 3B).

After 1 month of conservative treatment, the skin lesions improved with residual hyperpigmentation. No new lesions developed during the following 6 months (Figure 1B). Based on the histopathology and self-limited clinical course, she was diagnosed with RAE. (Figure 1B).

Discussion

In this report, we describe the first case of RAE following surgery in Taiwan. We propose that in this patient RAE is related to major surgery for perforated peptic ulcer, with hemodynamic change causing distal hypoxia. Likewise, the comorbidities of cardiovascular diseases, pneumonia, and peritonitis may have played roles in the development of RAE. RAE has been noted for its similarities in presentation to a wide spectrum of other conditions. Clinically, there

Table 1. **Etiology and coexistent diseases of RAE**

Systemic infection
Mainly subacute bacterial endocarditis
Local hypoxia and hemodynamic change
Peripheral vascular disease
Valvular cardiac disease
Renal disease
Postrenal transplantation
Autoimmune disease
Rheumatoid arthritis
Cryoglobulinemia
Lymphoproliferative disorder
Hepatitis
Cholesterol emboli
Arterio-venous shunt
Antiphospholipid syndrome
Chronic lymphatic leukemia
Dermal amyloid angiopathy

are multiple bluish-violaceous patches or plaques which are occasionally ulcerative or necrotic. The distribution of RAE is extensive but mainly occurs on the limbs.[3] To the best of our knowledge, the etiology of RAE is mainly due to coexistent diseases that result in occlusion or inflammation in the vascular system (Table 1). RAE after distal irrelevant surgery has not been previously reported.

RAE is characterized by intravascular endothelial proliferation. It is important to be aware of similar pathologic patterns associated with rapidly progressive and fatal malignant tumors such as Kaposi's sarcoma and angiosarcoma. We provide comparisons of these three conditions in Table 2. Comparing RAE with Kaposi's sarcoma histopathologically, the former is typically characterized by intravascular hyperplasia of endothelial cells with vascular proliferation in the dermis and subcutis. Fibrin-microthrombi in well-formed capillaries may also characterize RAE. Meanwhile, prominent spindle cells and slit-like vessels are present in Kaposi's sarcoma, accompanied by promontory sign, lymphoplasmacytic infiltration, and eosinophilic granules.4 Positive staining for CD31 and CD34 is consistent in both diseases. However, CD34 is only focally positive in RAE while strongly diffuse in Kaposi's sarcoma. Moreover, HHV-8 stains positively more often in Kaposi's sarcoma than in RAE, according to a case series study by McMenamin et al.[4] Regarding clinical course, cutaneous lesions spontaneously resolved with conservative treatment in our patient. Such self-limited clinical course is not observed in Kaposi's sarcoma.

Surgery for perforated peptic ulcer is not complicated and can be done within a short time. However, septic shock, bowel obstruction, hernia, intra-abdominal abcess, postoperative ileus, and pulmonary complications may occur. In our case, peritonitis and pneumonia were noted, which may have led to systemic inflammation and the precipitation of RAE.

The pathogenesis of RAE is not clearly understood, but immunologic factors and hypoxic stimulus may play a role. Among the many hypotheses proposed, the one that is most convincing is that RAE derives from vessel occlusion and tissue hypoxia that leads to vascular and endothelial proliferative changes. Once hypoxic stimulus stops, abnormal proliferation stops. Furthermore, active bleeding and operation may cause hemodynamic change(s), resulting in distal tissue hypoxia, which may also lead to RAE.

Semeraro *et al*. revealed that sepsis causes hemostatic problems with thrombocytopenia, hypercoagulable state, formation of thrombin and fibrin, and disseminated intravascular coagulation.[5] Salama *et al*. suggested that immunoglobulin deposition in vessels within the skin may be caused by a generalized hypersensitivity reaction. Subsequently, formation of thrombi contributes to local hypoxia and angiogenic factors from local cells result in neovascularization.[6] In our case, peritonitis and pneumonia brought about systemic inflammation. Indeed, experimental peritonitis-induced sepsis in an animal model has demonstrated alteration in cerebral microcirculation and tissue hypoxia.[7] In our case, microcirculation in the limbs may have been altered so as to induce hypoxia, ultimately bringing about RAE.

To sum up, we introduce a patient with coronary

Table 2. **Differential diagnoses of Kaposi's sarcoma, Angiosarcoma and RAE**

	Kaposi's sarcoma	Angiosarcoma	RAE
Predominant risk group (age/gender /race)	Age: >60 Gender: 3:1, male: female ratio Race: Mediterranean or Central/Eastern European Origin, Middle Eastern, Equatorial African males	Age: 65-70 Gender: 2:1 male: female ratio Race: Caucasian males	Age: middle age Gender: 1.3:1 male: female ratio Race: non-specific
Location	Most often on the oral mucosa, face (especially the nose), genitalia, and lower extremities	Most common on scalp and face, previously treated with radiation therapy	Spread throughout the body, but mainly on the limbs
Clinical manifestation	1. Purplish, reddish blue, or brown/black skin lesions (macules, nodules, plaques) on the lower extremities 2. Often accompanied by lymphedema	Blue or purple lesions (macular, nodular, or plaque) with hemorrhage or ulceration	Clinical presentation is often dramatic but not distinctive, including multiple erythematous tumors, plaques, macules, and ulcerated lesions with purpuric change
Pathology	Angiogenesis, inflammation, and spindle cell proliferation with diffuse slit like lumen formation, eosinophilic globules and some nuclear atypia	Pleomorphic spindle or epithelioid cells, often with bizarre or multinucleated forms; mitoses are evident	Firmly piling capillaries usually without endothelial atypia, and fibrin microthrombi in well-formed capillaries
Immuno-histochemistry stain	Positivity for HHV-8, Ki-67, D2-40, CD31, CD34. CD34 is strongly and diffusely positive	Positivity for vascular markers, such as the ERG transcription factor, CD31, CD34, and Factor VIII antigen	CD31 and focally positive for CD34 antibody-staining of spindle-shaped, round, or epithelioid cells, HHV-8(+ or -), and other endothelial markers
Treatment	Local: radiotherapy, excision, cryotherapy, laser ablation, intralesional or topical Systemic: chemotherapy: pegylated liposomal doxorubicin, vinblastine, paclitaxel, oral etoposide, vinorelbine, gemcitabine, and immunomodulators	Local: radiotherapy, neoadjuvant chemotherapy Systemic: taxanes (especially paclitaxel), doxorubincin	Treatment of the underlying condition/disorder may result in regression of RAE

artery disease who developed RAE after perforated peptic ulcer surgery accompanied by peritonitis and pneumonia. This is the first such case reported in Taiwan. Accordingly, physicians should be aware of postoperative and rapidly progressive lesions on the skin, especially in patients with cardiovascular disease. Since the clinical presentation of RAE is often dramatic but not distinctive and RAE shares histologic similarities with other conditions, early differentiation from malignant tumors such as angiosarcoma and Kaposi's sarcoma is crucial.

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