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Case Report

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Pyoderma gangrenosum: A paraneoplastic syndrome associated with occult colorectal malignancy? Report of a case and review of literature

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ABSTRACT

Introduction: Pyoderma gangrenosum (PG) is an uncommon sterile inflammatory neutrophilic dermatosis. Approximately 50% of PG patients have associated inflammatory bowel disease, rheumatic disorders or malignancies. Literature search reported only 2 cases of PG in association with colorectal cancer (CRC).

Case Report: A 74-year-old patient presented to the emergency department with central abdominal pain and vomiting for 24 hours. Recently, the patient was worked up for iron deficiency anemia and was due to have colonoscopy. She was also discovered to have multiple skin lesions on her left hand, which were ulcerated, erythematous, indurated, and thick with scaly plaque. Initially the differential diagnosis included: neutrophilic dermatosis, atypical mycoblastosis or mycosis. Skin biopsy revealed PG. The skin lesion did not respond to high-dose systemic steroids. Two months later during presentation to the emergency department with abdominal pain, abdominal and pelvic CT showed proximal sigmoid colon mass with nodular extension probably involving adjacent small bowel loops but no liver metastasis. Colonoscopy showed stenosing sigmoid mass, which was confirmed by biopsy to be adenocarcinoma. Laparotomy with resection of the sigmoid, upper part of the rectum, and a short segment of the involved small bowel was performed. Histology confirmed adenocarcinoma of the sigmoid (T4N0Mx). The skin lesions healed spontaneously following surgery.

Conclusion: Early treatment of CRC can enhance the outcome of patients with PG, which may point toward a related pathological process. Furthermore, PG may be an important predictor of CRC. We advise on detailed gastrointestinal tract GIT investigation for unresponsive PG.

Key words: *Pyoderma gangrenosum, colorectal cancer, paraneoplastic syndrome*

Introduction

Pyoderma gangrenosum is a chronic, debilitating, ulcerative, cutaneous disorder of unknown etiology. Associations with inflammatory bowel disease (IBD), lympho-proliferative disorders, and dermatoarthropathies such as rheumatoid arthritis and Behcet's syndrome are well described in the literature [1]. However, pyoderma gangrenosum as a primary manifestation of occult malignancy is rare [2–5].

Colorectal cancers account for 14% of commonly diagnosed invasive cancers in Australia. It is the second most common cancer accounting for 13% of cancer-related deaths, according to the Australian cancer registries [6]. We hereby report a case of a 74-year-old patient who presented with pyoderma gangrenosum and was found to have an occult sigmoid cancer. To best of

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our knowledge, this appears to be only the third such case and we present a brief review of the literature on the subject and its attendant management.

Case Summary

A 74-year-old female presented to the dermatology department with a non-healing ulcer over her left hand. She also mentioned a recent change in her bowel habits with no associated rectal bleeding. She denied any associated family history of IBD or gastrointestinal cancers. Clinical examination revealed 1–2-cm erythematous, scaly, indurated, pustular plaque lesions over the dorsum of both her hands (Figure 1). Her general and abdominal examinations were found to be unremarkable. Biopsies of the skin lesions revealed neutrophilic dermatoses with acute inflammatory cells and microabscesses suggestive of pyoderma gangrenosum. She was commenced on high-dose oral corticosteroids.

During a follow up visit after 2 months it was noticed that the skin lesions were not responding to treatment. Further investigations were carried out, including blood tests which revealed iron deficiency anemia for which a referral was made to our colorectal unit for further investigations including colonoscopy.

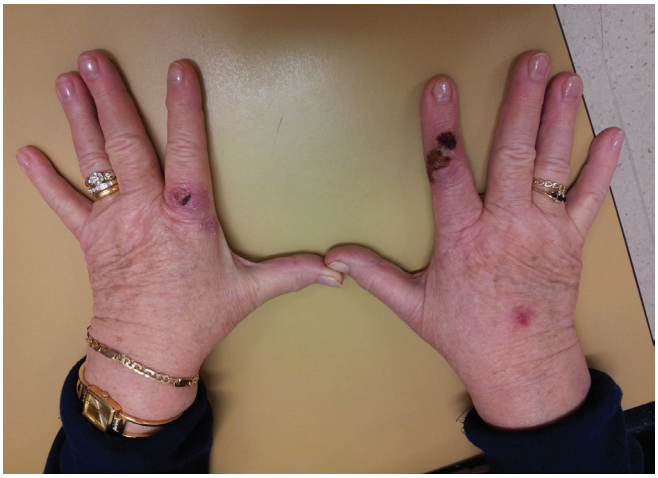

Figure 1. Cutaneous lesions over dorsum of both hands.

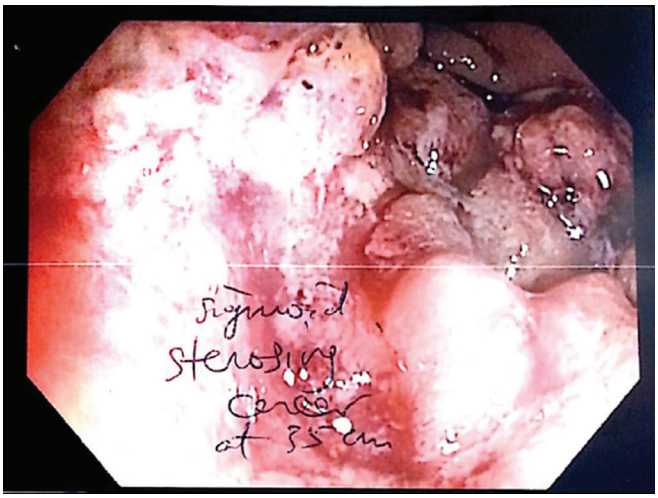

Figure 2. Colonoscopy images, stenosing sigmoid tumour.

Before having the colonoscopy, the patient presented to the emergency department with central abdominal pain and vomiting for 24 hours. Investigations showed elevated inflammatory markers and her stool was positive for occult blood. Abdominal and pelvic CT showed a proximal sigmoid colon mass with nodular extension probably involving adjacent small bowel loops but no liver metastasis.

Urgent colonoscopy showed a stricturing sigmoid tumour (Figure 2). Staging computed tomography confirmed the presence of the sigmoid mass with no associated distant metastases. Colonic biopsies confirmed moderately differentiated adenocarcinoma of the sigmoid.

She underwent an open high anterior resection with en bloc excision of a terminal ileal segment that was adherent to the cancer. Histology of the specimen showed a T4b, N0, M0 moderately differentiated adenocarcinoma of the sigmoid colon with no lymphovascular or perineural invasion.

Her post-operative recovery was uneventful and the skin lesions spontaneously healed following surgery. She is awaiting further oncology follow-up.

Discussion

Pyoderma gangrenosum is a rare non-infectious skin disorder with a reported incidence of 3 to 10 cases per million people per year [7]. The disease was first described by Brunsting et al. in 1930 and tends to affect young and middle aged adults between 20 and 50 years, with a high female preponderance [8,9]. It has a strong association in patients with inflammatory bowel disease (e.g., ulcerative colitis), rheumatological (e.g., rheumatoid arthritis) or haematological disorders (e.g., myelocytic leukaemia), and is thought to be immune-mediated although Arthus or Scwartzmann reaction with protein deposition in skin vessels has also been postulated [10]. Pyoderma gangrenosum secondary to drugs such as propylthiouracil, gemfinib (an epidermal growth factor receptor inhibitor) has also been described [11]. However, this cutaneous disorder as a primary manifestation of occult gastrointestinal neoplasia is rare.

Typically, lesions of pyoderma gangrenosum are seen as a pustule with an inflammatory base, an erythematous nodule, or a hemorrhagic bulla on a violaceous base. These lesions coalesce to form ulcers, and in some cases deep ulcers can expose underlying tendons, muscles, or nerves. Several ulcers may merge to form larger lesions that heal with atrophic pigmented cribriform scarring [1]. These lesions can appear in any part of the body but are predominantly seen over the pre-tibial areas. It is a clinical entity and histological examination of the lesion is complementary to the diagnosis. Knowledge of the patient's history for possible underlying disease and specific investigations based on that background are necessary.

Pyoderma gangrenosum is a type of neutrophilic dermatosis characterized by epidermal or dermal inflammatory infiltrates with neutrophils, with no signs of infection or vasculitis. Powell et al. described four clinical types of pyoderma gangrenosum: ulcerative, vegetative, pustular, and bullous lesions [12]. In the ulcerative variant of pyoderma gangrenosum, there is a massive dermal-epidermal neutrophilic infiltrate with abscess formation; in pustular pyoderma gangrenosum, a perifollicular neutrophilic infiltrate with subcorneal pustule formation; the bullous variant shows a neutrophilic infiltrate with intraepidermal vesicle formation; and in vegetative pyoderma gangrenosum, granulomatous reaction with peripheral palisading histiocytes and giant cells exists [1].

Differential diagnoses of pyoderma include vascular occlusive or venous calciphylaxis, deep mycosis, mycobacterial infections, herpes simplex, warfarin skin necrosis, drug eruptions, cutaneous malignancy and insect-bite reactions. Extracutaneous manifestations include involvement of respiratory mucosa, eyes, genital mucosa, splenic or pulmonary infiltrates, and neutrophilic myositis [11]. Pyoderma gangrenosum involving the prostate gland after radiotherapy for prostate cancer and following surgery for breast cancer have also been described in the literature [13,14].

Colorectal cancers typically manifest as haematochezia, changes in bowel habits, anemia, abdominal mass, weight loss, or with a strong familial predisposition. Patients can also present acutely with intestinal obstruction or with peritonitis due to visceral perforation. Atypical presentations include Streptococcus gallolyticus septicaemia, intestinal intussusception, infective spondylodiscitis, and as pyogenic liver abscesses [15-18]. Patients with longstanding inflammatory bowel disease (IBD) are at risk of bowel cancer, however pyoderma gangrenosum in the absence of IBD manifesting as colorectal malignancy has only been reported twice previously [3,4].

Paraneoplastic syndromes are consequences of occult cancers in the body, and are thought to be mediated by humoral factors and peptides excreted by tumor cells, or by a complement immune response against the tumour [19]. An array of cutaneous granulomatous disorders have been found to be associated with internal malignancy. Among them, sarcoidosis, granuloma annulare, psoriasis, pyoderma gangrenosum, or other neutrophilic dermatoses such as the Sweet syndrome and subcorneal pustular dermatosis may precede the development of a neoplastic process by months or years [20]. Cellular analysis in pyoderma demonstrates aberrant integrin oscillations on neutrophils. Pathways to protect the epidermis from neutrophil infiltration appear to be insufficient resulting in tissue necrosis [21]. Pyoderma gangrenosum exhibits the Koebner phenomenon, also called the 'Koebner response' or the 'isomorphic response', which refers to skin lesions appearing on lines of trauma [22].

Baseline tests, such as full blood count, liver and renal function tests, erythrocyte sedimentation rate (ESR), and chest X-ray (CXR) are useful in the initial diagnostic work-up of these patients. Advanced investigations such as computed tomography or gastrointestinal endoscopy are warranted in patients with a history of refractory lesions and/or with a high clinical suspicion of underlying neoplasm. In our patient, pyoderma with iron deficiency anemia prompted a colonoscopy that picked up her colonic malignancy.

Treatment of pyoderma gangrenosum includes local and/or systemic therapy. Local measures involve topical or intra-lesional glucocorticoids and can be supplemented with oral corticosteroids such as prednisolone. In refractory lesions, treatment options include dapsone, thalidomide, azathioprine, 6-mercaptopurine, mycophenolate mofetil, cyclophosphamide, cyclosporine, and tacrolimus. Other agents used re-

cently are tumour necrosis factor alpha (TNFα) inhibitors such as infliximab and related agents, which have shown good clinical responses [11]. Surgery to the cutaneous lesion(s) has to be considered cautiously as it can trigger new lesions or promulgate the situation. Autologous split skin grafts or novel therapy such as bioengineered skin, like the dermal regeneration template Integra®, hair follicle stem-cell-derived autologous keratinocyte sheets Epidex® or hyaluronic acid-based autologous keratinocyte delivery system Laserskin® are some of the surgical options that have been reported in the literature [11]. Continued surveillance of these patients is necessary, since the malignancy may not be immediately detectable. Some of the cutaneous paraneoplastic syndromes will respond to specific measures, such as systemic corticosteroid therapy, but for the most part, successful resolution requires eradication of the underlying malignancy [23].

Conclusion

Pyoderma gangrenosum is a rare paraneoplastic syndrome and its association with colorectal malignancy is rare. A high index of suspicion and a need for prompt gastrointestinal evaluation cannot be overemphasized. Treatment of the primary malignancy results in resolution of pyoderma gangrenosum, however continued surveillance is recommended.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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