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Subcutaneous Metastatic Adenocarcinoma: An Unusual Presentation of Colon Cancer – Case Report and Literature Review

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Key Words
Colorectal cancer · Subcutaneous metastasis · Cutaneous metastasis

Abstract
Subcutaneous metastasis from a visceral malignancy is rare with an incidence of 5.3%. Skin involvement as the presenting sign of a silent internal malignancy is an even rarer event occurring in approximately 0.8%. We report a case of a patient who presented to her dermatologist complaining of rapidly developing subcutaneous nodules which subsequently proved to be metastatic colon cancer, and we provide a review of the literature.

Introduction

The incidence of subcutaneous metastasis from a visceral malignancy, excluding malignant melanoma, lymphoma, and leukemia, is rare with an incidence of 5.3% [1]. Skin involvement as the presenting sign of a silent internal malignancy is an even rarer event occurring in approximately 0.8% [2]. We report a rare case of a patient who presented to her dermatologist complaining of rapidly developing subcutaneous nodules which subsequently proved to be metastatic colon cancer, and we provide a review of the literature.

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Case Report

A previously healthy 44-year-old Caucasian female was referred to dermatology with a 5-week history of rapidly growing subcutaneous nodules on her back, chest, breasts, abdomen, axillae and thighs (fig. 1). Except for fatigue, the review of systems was unremarkable. Numerous 0.5–3-cm, well-defined, mobile, firm and slightly tender subcutaneous nodules without overlying epidermal changes were noted on physical examination. Results of a punch biopsy revealed a poorly differentiated adenocarcinoma that was cytokeratin (CK)-7 negative, CK-20 positive, TTF-1 negative, and Cam 5.2 positive, suggestive of metastasis from the lower gastrointestinal tract (fig. 2). A CT scan was obtained which showed circumferential thickening of the cervix, innumerable subcutaneous masses, sigmoid colonic wall thickening, and extensive retroperitoneal and intra-abdominal adenopathy, with suspicion of metastatic disease (fig. 3). Significantly, there was no notable liver involvement. Pelvic examination was unremarkable, but colonoscopy revealed a 4-cm, fungating, non-obstructing sigmoid mass. Given the extent of the disease and the lack of obstructive symptoms a tunneled catheter was placed and the patient began systemic therapy with FOLFOX plus bevacizumab. Approximately 3 weeks after initiation of systemic therapy the patient presented with bowel perforation and underwent abdominal exploration, sigmoid resection and end-colostomy. At laparotomy a perforated colonic mass was noted with peritoneal disease along the root of the small bowel mesentery without evidence of hepatic metastasis. Final pathology returned a poorly differentiated T4, N2, M1 adenocarcinoma with signet ring cell and focal mucinous features, and lymphovascular and perineural invasion. Subsequent testing revealed the tumor to be wild-type for KRAS and microsatellite stable.

Initially, the patient showed improvement in both the number and size of the subcutaneous metastases. However, at the time of her fourth cycle of FOLFOX, some of the lesions began to progress. Subsequent CT scan confirmed progression of disease and while FOLFORI plus panitumimab were considered for the patient, she had rapid physical decline, intermittent infections, and therefore only received one dosage of panitumimab before deciding to go home under care of nurses. She died approximately 1 week later.

Discussion

There is significant variability in reports on the incidence of cutaneous metastasis from visceral primaries, some finding it to be as low as 0.7%, while others find it as high as 9%. Larger series have reported an average incidence of 5% [1–4]. Lookingbill et al. [2] retrospectively reviewed 7,316 tumor registry patients and reported an overall 5% incidence of cutaneous metastasis, a number which almost doubled (9.6%) when only patients with known metastatic disease were considered. Ninety-two patients (1.3%) presented with cutaneous involvement at the time of diagnosis, 59 (0.8%) of whom had skin involvement as the first presenting sign [2]. Of these, 42 (71%) were locoregional metastasis and only 17 (29%) were considered true distant metastases [2]. Cutaneous involvement from a colorectal cancer primary accounted for only 18 (2.3%) patients. Among these cases, 4 (22%) were present at the time of diagnosis and 3 (16%) were the chief complaint which prompted the search for the primary [2]. The largest meta-analysis to date by Krathen et al. [1], which included both autopsy series and tumor registries (n = 20,380), reported an incidence of 5.3% (n = 1,080). The tumor with the highest incidence of cutaneous metastasis by far was breast cancer (24%), followed by renal (4%), ovarian (3.8%), lung (3.6%), colorectal (3.4%), and prostate cancer (0.7%) [1]. The most common site for metastasis was the chest (28.4%), followed by the abdomen (20.2%), extremities (12%), neck (11%), back (11%), scalp (7%), pelvis (6%), and the face (5%) [1].

The identification of cutaneous metastasis from a visceral malignancy is an ominous finding which usually signifies widespread disease and portends a poor prognosis [5, 6]. Lookingbill et al. [5] in a retrospective study of 4,020 patients found that after recognition

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of skin metastases, mean survival ranged from 1 to 34 months depending on the primary tumor. An average survival of 18 months was noted in patients with skin metastasis from colorectal carcinoma [5]. Schoenlaub et al. [6] retrospectively reviewed 200 cases of patients with evidence of cutaneous metastasis from a visceral primary and found the median survival to be 6.5 months. Patients with an underlying colorectal primary fared even worse with a median survival of 4.4 months [6].

The mechanism of cutaneous metastasis from colorectal cancer is poorly understood but can conceptually be explained. After the initial malignant transformation of colonic mucosal cells, neovascularization occurs, a process fostered by the production of vascular endothelial growth factors, platelet-derived growth factors, and basic fibroblast growth factors [7]. Alterations in cell adhesion prompted by a loss of E-cadherin expression allow the malignant cell to interact with the extracellular matrix which it degrades, remodels and subsequently invades [8]. Tumor cells attach and migrate along the extracellular matrix via receptor-ligand interactions eventually intravasating lymphatics and venules, facilitating lymphatic and hematogenous metastasis. While once considered a passive course, 'tumor embolization' is now thought to be mediated by lymphangiogenic and angiogenic growth factors which help to increase the total vessel surface area available for invasion, increase the pumping action of draining afferent lymphatic vessels and induce lymphangiogenesis and angiogenesis in preparation for metastasis [8, 9]. Following intravasation, cells which survive the mechanical stress of circulation and the innate immune system eventually colonize the subcutaneous tissues and lay dormant until they acquire the necessary angiogenic properties, mutations of metastasis virulence genes, or microenvironmental changes which prompt their emergence from dormancy [8, 10].

Conclusion

In summary, cutaneous metastasis from a colorectal primary is a rare event. When present, the metastasis usually signifies disseminated disease and poor prognosis. Further analysis of the biology of this mode of metastasis may shed light on mechanisms of metastasis to specific organs, and hopefully these findings will provide targets for novel targeted therapeutic intervention.

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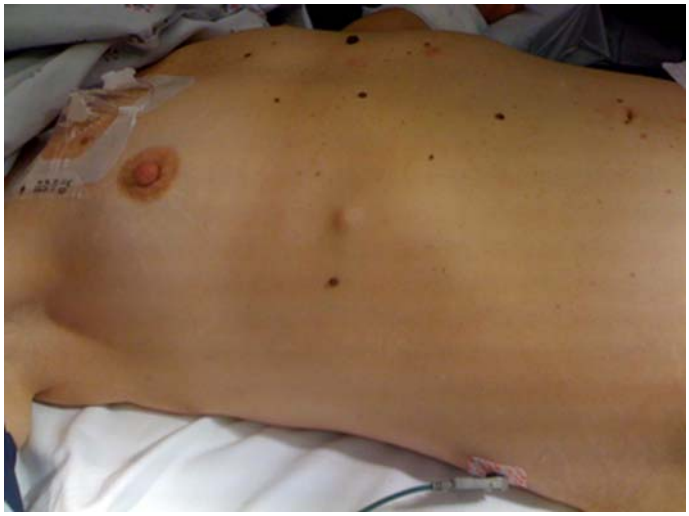

Fig. 1. Subcutaneous metastatic nodules.

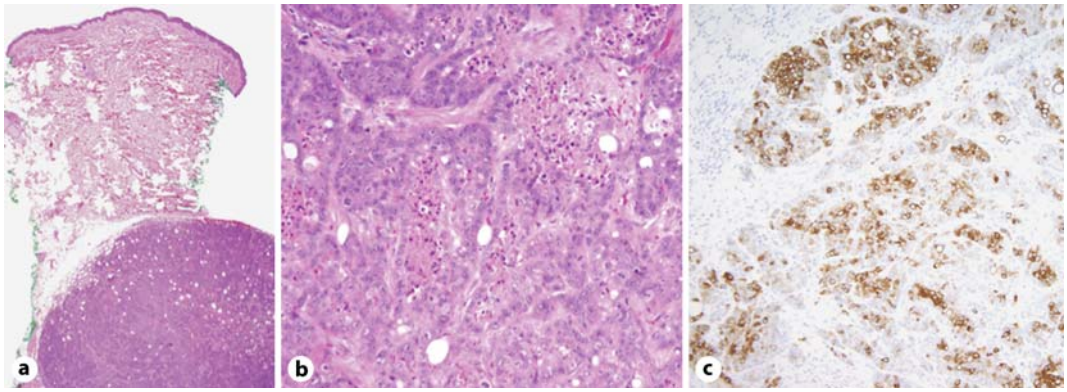

Fig. 2. **a** Biopsy showed subcutaneous nodule of metastatic adenocarcinoma (hematoxylin-eosin, original magnification ×20). **b** The proliferation consisted of glands with atypical epithelial cells, mitoses, and central luminal 'dirty necrosis' which is suggestive of a colon primary (hematoxylin-eosin, original magnification ×400). **c** CK-20 immunostain highlights the cells further supporting a colon primary (hematoxylin-eosin, original magnification ×100).

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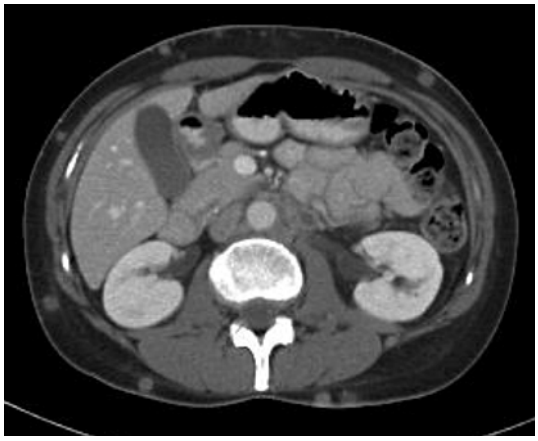

Fig. 3. CT scan of subcutaneous metastatic nodule.

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