Unexpected outcome (positive or negative) including adverse drug reactions

Pleomorphic malignant histiocytoma: a rare skin cancer in a patient on azathioprine for ulcerative colitis

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Summary

A 67-year-old female who was diagnosed with ulcerative colitis in 2001, presented with a soft tissue mass in the middle of her back of 4 months duration in April 2011. It was excised; however it recurred at the same site in September 2011. Wide excision of the mass was done. Pathology revealed T1aNxM0 pleomorphic malignant fibrous histiocytoma or undifferentiated pleomorphic sarcoma. Whole body bones scan and staging CT scan of the chest, abdomen and pelvis was negative for distant metastasis. She received local radiotherapy at the site of excision. No chemotherapy was given.

BACKGROUND

Sarcomas constitute only one per cent of adult cancers with malignant fibrous histiocytoma (MFH) being the most common. Review of literature shows an increased risk of non-melanoma skin cancer in patients with inflammatory bowel disease. The most common being squamous cell and basal cell carcinoma. The risk increases even further in organ transplant patients and those who are on immunosuppressive treatment including azathioprine.

There are no case reports of MFH in a patient with ulcerative colitis on azathioprine as it is a rare skin cancer.

Recently, Sabesan *et al* reported 5-year survival rate of MFH as 48%. The clinical course being even worse for patients with tumours extending into bony structures.¹

Is there a need for education programs for patients with inflammatory bowel disease regarding avoidance of sun and use of sun protective clothes? Would there be any benefit of regular skin cancer screening guidelines in this patient population remains a question.

CASE PRESENTATION

A 67-year-old Caucasian female was diagnosed with ulcerative colitis in 2001 when she presented with a 4-month history of bloody stool and abdominal cramps. She was initially treated with oral/rectal mesalamine and corticosteroids therapy. However, her symptoms recurred in 9 months and she was started on a stable dose of azathioprine, 150 mg once daily. She had no recurrence of symptoms of ulcerative colitis on azathioprine. She had history of high blood pressure for which she was on hydrochlorothiazide and atenolol. Most of her visits to the doctor after 2001 were follow-up visits for her blood pressure management.

In January 2011, she noticed a cyst located on the mid back, which continued to increase in size. It was excised in April. Unfortunately, tissue was not sent for pathology. The cyst recurred in September. Laboratory examination was unremarkable. The excision pathology revealed T1aNxM0 pleomorphic MFH or undifferentiated pleomorphic sarcoma. Resection with wide excision of the cyst

was done followed by radiotherapy. Immunohistochemical stains AE1/3, S100 protein, HMB45, desmin, CD31 were all negative. Her whole body bones scan and staging CT scan of chest, abdomen and pelvis was negative for distant metastasis. No chemotherapy was given.

She was a non-smoker with no history of significant sun exposure. There was no family history of cancer.

INVESTIGATIONS

MFH is diagnosed by skin biopsy like any other skin cancer. It is characterised by a storiform or cartwheel-like growth pattern. (figures 1 and 2).

The diagnosis of MFH depends on an accurate differential diagnosis from other sarcomas, observation of karyomorphism and differential figures, and positive results on immunohistological staining. It was reported that MFH frequently expresses vimentin, actin, CD-68, and α 1-antitrypsin and α 1-antichymotrypsin.²

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of MFH should include pleomorphic liposarcoma and rhabdomyosarcoma.³

TREATMENT

The primary therapeutic modality for MFH is surgery, but because of high rates of local and distant recurrence, radiation therapy should be added to decrease local relapse. Role of chemotherapy is unclear.³

OUTCOME AND FOLLOW-UP

Inadequate removal of the tumour is associated with a high recurrence rate of 20% to 42%.⁴ In this case report there has been no recurrences of the tumor in six months based on outpatient follow-up visits.

DISCUSSION

One in five Americans develops skin cancer, which accounts for one third of all cancers in the USA. Cancers that develop

Figure 1 Intermediate view. Histological specimen showing classic storiform- pleomorphic malignant fibrous histiocytoma. Microscopically, storiform pattern shows short fascicles of spindle cells radiating from a central portion which is intermixed with neoplastic giant cells in the pleomorphic portion.

from melanocytes, the pigment-making cells of the skin, are called melanomas. The non-melanoma skin cancers are grouped differently as they behave differently than the melanoma skin cancers. Keratinocyte cancers are the most common non-melanoma skin cancers. They include basal cell carcinoma, squamous cell carcinoma. Other less common types of non-melanoma skin cancer, which are quite different from keratinocyte cancers and are treated differently, include Merkel cell carcinoma, Kaposi sarcoma, cutaneous lymphoma, skin adnexal tumours and various types of lymphoma. Sarcomas are rare neoplasms, constituting only 1% of all cancers. There are two main types of sarcoma: bone sarcomas and soft tissue sarcomas. Soft tissue sarcomas can develop from soft tissues like fat, muscle, nerves, fibrous tissues, blood vessels or deep skin tissues. The most common types of sarcoma in adults are MFH and liposarcoma. In the extremities, MFH is the most common type.⁵

The term MFH or pleomorphic undifferentiated sarcoma was first introduced in the early 1960s to refer to a group of soft tissue tumours, characterised by a storiform or cartwheel-like growth pattern.^{6,7} These tumours do not commonly manifest in the head and neck region, except in the paediatric population. Head and neck sarcomas represent only 2% to 15% of all adult sarcoma cases.^{8–10} They can be benign or malignant. Lymph node metastases occur in only 3% to 10%. Distant metastases occur in 25–35% of the patients at diagnosis.¹¹ The most frequently involved site is the lung followed by bone, central nervous system and liver.^{12,13} Known risk factors for skin cancers include lighter skin, family or personal history of skin cancer, ultraviolet (UV) sun exposure, advancing age.^{14,15}

A study published in British Journal of cancer showed that immunosuppression in patients with autoimmune

conditions can be a risk factor for certain cancers. The most common autoimmune disorders were rheumatoid arthritis which was associated with Merkel cell carcinoma, ulcerative colitis with Kaposi's sarcoma, non-Hodgkin's lymphoma with Merkel cell carcinoma.¹⁶

Ulcerative colitis is a chronic inflammatory disorder of the gastrointestinal tract that affects the large bowel. The incidence of ulcerative colitis is 1.2 to 20.3 cases per 100 000 persons per year, and its prevalence is 7.6 to 246.0 cases per 100 000 per year, as compared with an incidence of 0.03 to 15.6 cases and a prevalence of 3.6 to 214.0 cases per 100 000 per year for Crohn's disease.¹⁷ Classical symptoms of ulcerative colitis include bloody diarrhoea due to mucosal inflammation of rectum (proctitis) sometimes spreading to the rest of the colon. In addition to the various local complications involving the colon, there are several extra intestinal manifestations involving the musculoskeletal, ocular, hepatobiliary, haematopoietic and coagulation system. The common skin manifestations include erythema nodosum and pyoderma gangrenosum.¹⁷ Patients with xeroderma pigmentosa, exhibit extreme sun sensitivity, and increased risk to develop UV-induced skin cancer.¹⁸ Autoimmunity may play a role in ulcerative colitis. The extra intestinal manifestations are due to circulating IgG1 antibodies against the antigens on colonic epithelium which cross react with antigens shared with skin, eye, joints and biliary epithelium. Tropomyosin 5, a structural protein, is the putative target auto antigen of the IgG1 antibodies, but evidence of classical antibody-mediated autoimmunity in ulcerative colitis is still lacking.¹⁷

First line treatment for ulcerative colitis is sulfasalazine and its 5-amino salicylate derivatives (mesalamine,

Figure 2 Higher magnification shows spindle cells. Mitotic figures can also be seen, as highlighted.

olsalazine, and balsalazide) given by oral or rectal route which if not effective, rectal steroids followed by oral glucocorticoids can be used to achieve remission. In case of lack of response to glucocorticoids, infliximab, a monoclonal antibody against tumour necrosis factor (TNF- α), in combination with azathioprine can be used. The combination has been shown to be superior to monotherapy in order to induce glucocorticoid-free remission.¹⁷ Once remission is achieved, the glucocorticoids can be discontinued and they are maintained in remission on 5-aminosalicylate or azathioprine. The glucocorticoid-free remission is significantly higher with azathioprine than with 5-aminosalicylate. Azathioprine should be continued life long as its withdrawal is associated with risk of relapse.¹⁹ Mercaptopurine is a safe alternative in patients with digestive intolerance or hepatotoxicity due to azathioprine.

Patients treated with azathioprine have a reduced minimal erythema dose (lowest amount of radiation required to produce erythema 24 h after irradiation) for UVA light, but not UVB light. The active metabolite of azathioprine is 6-mercaptopurine, which incorporates into DNA after converting into 6-thioguanine. On photochemical activation of DNA, 6-TG triggers protein and DNA oxidation resulting in DNA mutations. Upon exposure to UVA, it converts into guanine-6-sulfonate, which blocks RNA polymerase II. This leads to lethal transcription arresting DNA lesions and mutations.¹⁸ There is selective sensitivity to UVA in azathioprine treated patients. UVA light makes up a majority of incident midday solar radiation however UVB rather than UVA exposure is responsible for the carcinogenic effects of ultraviolet radiation. This underscores the need

for further studies which elucidate the biological mechanism responsible for this association.^{20, 21}

A retrospective cohort and nested case-control study was conducted with the aim to evaluate the risk of non-melanoma skin cancer (NMSC) in patients with or without inflammatory bowel disease (IBD) and to evaluate the risk of non-melanoma skin cancer in patients who use immunosuppressive medications or biological anti-TNF therapies as compared to people who do not use these medications. The class of medications included azathioprine and 6-mercaptopurine (thiopurine class), methotrexate, tacrolimus and cyclosporine (calcineurin class), mycophenolate mofetil, infliximab and adalimumab (biologic class). The study showed an increased incidence of NMSC in patients with IBD, and especially among those on immunosuppressive medications such as thiopurines. However, there were some drawbacks of the study one of which was the inability to distinguish between basal cell and squamous cell skin cancers. This study included people less than 64 years of age, and since the risk of skin cancers is shown to increase with age, the actual correlation might be underestimated.²²

There are known cases of non-melanoma skin cancers including squamous and basal cell carcinoma in patients with inflammatory bowel disease on immunosuppressive therapy, which are the most common skin cancers. This is a rare case of MFH in a patient with ulcerative colitis on a standard dose of azathioprine for 10 years to maintain remission.

There is no skin cancer screening guidelines or programs for behaviour alteration including skin protection in

patients with inflammatory bowel disease on immunosuppressive therapy that would decrease the incidence of skin cancer.

Learning points

- ▶ The non-melanoma skin cancers are grouped differently from melanoma skin cancers as they behave differently than the melanoma skin cancers. Keratinocyte cancers are the most common non-melanoma skin cancers, which include basal cell carcinoma, squamous cell carcinoma. Sarcomas are one of non-keratinocyte non-melanoma skin cancers, which are as rare as one per cent of all cancers. The most common types of sarcoma in adults are MFH.
- ▶ Soft tissue sarcoma can be benign or malignant. Distant metastases occur in 25–35% of the patients at diagnosis.
- ▶ Known risk factors for skin cancers include family or personal history of skin cancer, ultraviolet sun exposure, advancing age and immunosuppression.
- ▶ Azathioprine should be continued life long for patients with ulcerative colitis as its withdrawal is associated with risk of relapse.

Competing interests None.

Patient consent Obtained.

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