Exceptional Case

Muir–Torre syndrome in a haemodialysis patient

Evonne D. Godfrey1, Robert A. Coward1, Deepa Gharpuray-Pandit2, Fiona Lalloo3, Stuart McKirdy4 and Alexander Woywodt1

1Department of Renal Medicine, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, Lancashire, UK, 2Department of Pathology, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, Lancashire, UK, 3Genetic Medicine, St Mary’s Hospital, MAHSC, Manchester, UK and 4Plastic Surgery, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, Lancashire, UK

Correspondence and offprint requests to: Alexander Woywodt; E-mail: alex.woywodt@lthtr.nhs.uk

Abstract

Muir–Torre syndrome (MTS) is a rare inherited cancer syndrome with variable penetrance. MTS follows an autosomal-dominant pattern of inheritance, and is a subtype of Lynch syndrome (formally known as hereditary non-polyposis colorectal cancer (HNPCC)). MTS is caused by mutations in one of several mismatch repair genes. Patients typically present with sebaceous neoplasms (sebaceous adenoma, sebaceous epithelioma, or sebaceous carcinoma) or with multiple keratoacanthomas. These patients also have an increased lifetime risk of visceral malignancies, typically affecting the colon, ovary, endometrium, genitourinary tract and small bowel. We describe a case of MTS in a haemodialysis patient and implications for transplant listing.

Keywords: Muir–Torre syndrome; sebaceous cell carcinoma

Background

Malignancy is believed to be more common in patients with end-stage renal failure than in matched controls with normal renal function [1]. However, the role of cancer screening, if any, in maintenance dialysis patients remains unclear [2, 3]. Most cases of cancer in end-stage renal disease (ESRD) are picked up when they cause symptoms. Of note, these patients have above average exposure to doctors and organ imaging [4], resulting in the detection of asymptomatic malignancies [5]. In contrast, a diagnosis of malignancy in the context of an inherited cancer syndrome is exceedingly rare. We report the interesting case of a middle-aged dialysis patient who presented with recurrent sebaceous tumours and who was eventually diagnosed with Muir–Torre syndrome (MTS), a rare genetic cancer syndrome.

Case

A 45-year-old Asian female haemodialysis patient with underlying IgA nephropathy presented in 2009 with a 25-mm non-pigmented nodular lesion on her left shoulder. The patient had felt the lesion was probably non-specific and harmless. Of note, a 4 × 5 mm benign sebaceous epithelioma of the abdominal skin had been resected in 2007. At the time of her current presentation the patient was systemically well and asymptomatic. The patient was then referred to a surgeon for what appeared to be a simple sebaceous cyst and the lesion was removed. Histology showed a tumour with sebaceous differentiation, frequent and atypical mitoses and infiltration of the surrounding tissues (Figure 1). A diagnosis of sebaceous carcinoma was made. Wide excision was carried out and histology showed clear margins. Computed tomography of chest and abdomen showed no metastasis. The patient was suspended from the renal transplant waiting list and a literature search was performed, since none of the clinicians involved had ever encountered this malignancy before. MTS was suspected after reading one of the first references [6] retrieved in Google™. The patient was referred to the regional clinical genetics service. A three-generation family tree was taken which demonstrated that her father had been diagnosed with a sebaceous carcinoma at the age of 50 years, a squamous cell carcinoma at 51 years, colon carcinoma at 52 years and rectal carcinoma at 54 years. Her paternal aunt had endometrial carcinoma at 56 years, her cousin had endometrial carcinoma at 47 years and a further cousin was diagnosed with ovarian cancer at 41 years (Figure 2). This fulfilled the Amsterdam criteria for Lynch syndrome [7] and the clinical diagnosis of MTS, a subset of Lynch syndrome, was made. This was confirmed by the identification of a pathogenic mutation in MSH2. Colonoscopy was normal. Prophylactic hysterectomy and bilateral salpingo-oophorectomy were carried out in July 2010, without evidence of malignancy. Since then, the patient has had various benign sebaceous neoplasms resected until in April 2012, another 15-mm sebaceous cell carcinoma on the patient’s back was resected. Again, wide excision was carried out in May 2012, and resection margins were clear. The patient is currently well and without evidence of recurrence or metastasis. She remains suspended on the transplant waiting list.
mitoses (arrows) (×600).

prolong the exposure to carcinogenic substances, which play a role and it has been suggested that renal failure may persist after renal transplantation [13]. Smoking may also dispose to renal cell carcinoma [12]. This increased risk increased rate of some malignancies. One factor is surely due to increased sun exposure [11].

dermal patients in Asia [10], presumably due to increased exposure to viral disease. In contrast, squamous cell carcinoma of the skin is very common in Australia, most likely exposure to sun. In Australia, squamous cell carcinoma is the most common skin cancer, followed by sebaceous carcinoma [9].

Fig. 1. Sebaceous carcinoma. (A) The tumour shows a lobular pattern, with predominantly peripheral basaloid cells. Centrally sebocytes are also seen (×40). (B) High-power view demonstrating basaloid cells with numerous mitoses (arrows) (×600).

Discussion

Several studies have observed an increased incidence of malignancies in patients with ESRD [1, 8] although the magnitude of the effect appears to be moderate [1]. Malignancies that appear to be more common in ESRD than in matched controls with normal renal function typically include renal cell carcinoma and urothelial cancer [9], whereas cancer of the lung, colon and rectum, prostate, breast, and stomach were not increased in the largest study reported to date [8]. There are interesting geographical differences as well, with a higher incidence being observed in Australia and New Zealand, followed by the USA and Europe [5]. The pattern of cancers also varies, often in accordance with well-described risk factors. For example, hepatocellular carcinoma is more common in dialysis patients in Asia [10], presumably due to increased exposure to viral disease. In contrast, squamous cell carcinoma of the skin is very common in Australia, most likely due to increased sun exposure [11].

It is not entirely clear why ESRD associates with an increased rate of some malignancies. One factor is surely the occurrence of acquired cystic kidney disease, which predisposes to renal cell carcinoma [12]. This increased risk persists after renal transplantation [13]. Smoking may also play a role and it has been suggested that renal failure may prolong the exposure to carcinogenic substances, which undergo glomerular filtration [14]. Other factors that have been invoked include oxidative stress and deficient DNA repair mechanisms [14].

We describe an interesting case of MTS in a female haemodialysis patient. We only arrived at the diagnosis when one of us suspended the patient from the renal transplant list, following her first presentation with sebaceous cell carcinoma, googled the words ‘sebaceous carcinoma’ and noted the association of this particular malignancy with MTS. Others have described this approach previously [15]. Referral to the regional genetic service confirmed the diagnosis.

MTS is an autosomal-dominant disease named after London surgeon Edward Grainger Muir [16] and New York dermatologist Douglas Torre [17] who first described cases in the 1960s. MTS is often diagnosed late due to its presentation with seemingly benign sebaceous cysts around the eyelids and, less frequently, other areas of the skin [18]. After the sebaceous carcinoma has manifested in MTS, nearly half of the individuals are estimated to develop two or more malignancies before, after or simultaneously with the initial tumour. The most common neoplasms connected to MTS are colorectal (proximal to or at the splenic flexure) and genitourinary [19]. MTS is caused by mutations in the mismatch repair genes, in particular MLH1 and MSH2, although mutations in MSH6 have also been described [20]. MTS is therefore recognized as a subset of Lynch syndrome. Regarding screening, the major risk to patients is 60–80% lifetime risk of bowel cancer and up to 60% of endometrial cancer. There are various suggestions of screening for endometrial and colon cancer (1–3 years depending on the mutation) with hysterectomy and bilateral oophorectomy largely preventing the development of endometrial and ovarian cancer [21]. Screening of MTS-associated skin lesions in patients with Lynch syndrome has been recommended with annual dermato logical examination [22] and with screening protocols based on those used for Lynch syndrome [23]. The skin lesions are often situated in either the pericu lar or extraocular regions. These two categories of sebaceous carcinoma are less often associated with MTS than extraocular [24]. Periocular skin lesions can be mistaken for chalazion or blepharoconjunctivitis [25]. Extraocular lesions are less common, more likely to be malignant and aggressive in their clinical behaviour. Histologically, it can be difficult to distinguish between benign and malignant sebaceous tumours. The former show a lobular organization and feature peripheral basaloid cells, which are usually more than two cell layers thick [20]. High-power view will show mature sebocytes showing foamy cytoplasm and central nuclei. Mitoses are scanty and cellular atypia is minimal. In contrast, sebaceous carcinomas show pleomorphic enlarged basaloid cells showing significant atypia with frequent and atypical mitoses [21]. Foci of necrosis and infiltrative growth may also be seen. Only scanty mature sebocytes are seen.

The management of sebaceous carcinoma is surgical with wide excision. Radiotherapy is used in extensive disease. To our knowledge no chemotherapy has proved effective on the tumour [26]. There are anecdotal reports to suggest that isotretinoin and interferon alpha-2a may prevent the occurrence of new lesions [27].

Finally, a diagnosis of MTS has implications for a patient on the transplant list, although, due to the rarity of the syndrome, there are no data from which to draw recommendations. Levi et al. described the case of a
55-year-old man 5 years after renal transplantation who presented with sebaceous carcinoma, leading to a diagnosis of MTS. Switching his immunosuppressive treatment to a sirolimus-based regime resulted in halting new lesions [28]. Others have emphasised that sebaceous tumours can occur in transplant patients without MTS [29]. We felt it difficult to recommend transplantation in a patient with a genetic cancer syndrome and after several malignant tumours had already been diagnosed. However, individuals with MSH2 mutations who are compliant with the surveillance programme have a normal life expectancy. We presented the case to the Israel Penn International Transplant Tumour Registry (IPITTR), who recommended a 5-year suspension from the waiting list.

Conclusion

MTS is a rare inherited cancer syndrome. A high degree of suspicion should be employed by pathologists [30] and clinicians when patients present with recurrent sebaceous tumours. Clinicians need to take a full family history, in particular asking about a history of bowel and endometrial cancer. These patients should be referred to genetic services to investigate the family appropriately and if found to have an mismatch repair gene mutation, enter a surveillance programme. This would include dermatological surveillance, regular colonoscopies and hysteroscopies in women. The diagnosis of MTS in a patient with ESRD also mandates a discussion of transplant listing, taking into account the extent of sebaceous malignancies but also the predisposition to malignancy in general.

Acknowledgements. We are indebted to the Israel Penn International Transplant Tumour Registry for advice regarding suspension on the waiting list.

Conflict of interest statement. None declared.

References

1. Maisonneuve P, Agodoa L, Gellert R et al. Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet 1999; 354: 93–99
2. Holley JL. Screening, diagnosis, and treatment of cancer in long-term dialysis patients. Clin J Am Soc Nephrol 2007; 2: 604–610
3. Wong G, Turner RM, Chapman JR et al. Time on dialysis and cancer risk after kidney transplantation. Transplantation 2013; 95: 114–121
4. De Mauri A, Brambilla M, Chiarinotti D, Matheoud R, Carriero A, De Leo M. Estimated radiation exposure from medical imaging in hemodialysis patients. J Am Soc Nephrol 2011; 22: 571–578
5. Stewart JH, Vajdic CM, van Leeuwen MT et al. The pattern of excess cancer in dialysis and transplantation. Nephrol Dial Transpl 2009; 24: 3225–3231
6. Alzaraa A, Ghafoor I, Yates A, Dhebri A. Sebaceous carcinoma of the skin of the breast: a case report. J Med Case Rep 2008; 2: 276
7. Vosen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPPC, Lynch syndrome) proposed by the International Collaborative group on HNPPC. Gastroenterology 1999; 116: 1453–1456
8. Matas A, Kjellstrand C, Simmons R, Buselmeier T, Najariz J. Increased incidence of malignancy during chronic renal failure. Lancet 1975; 305: 883–886
9. Stewart JH, Bucchiotti G, Agodoa L et al. Cancers of the kidney and urinary tract in patients on dialysis for end-stage renal disease: analysis of data from the United States, Europe, and Australia and New Zealand. J Am Soc Nephrol 2003; 14: 197–207
10. Lin HF, Li YH, Wang CH, Chou CL, Kuo DJ, Fong TC. Increased risk of cancer in chronic dialysis patients: a population-based cohort study in Taiwan. Nephrol Dial Transpl 2012; 27: 1585–1590
11. Ramsay HM, Fryer AA, Hawley CM, Smith AG, Nicol DL, Harden PN. Factors associated with nonmelanoma skin cancer following renal transplantation in Queensland, Australia. J Am Acad Dermatol 2003; 49: 397–406
12. Hoshida Y, Nakanishi H, Shin M, Satoh T, Hanai J, Aozasa K. Renal neoplasias in patients receiving dialysis and renal transplantation: clinico-pathological features and p53 gene mutations. *Transplantation* 1999; 68: 385–390
13. Schwarz A, Vatondaslar S, Merkel S, Haller H. Renal cell carcinoma in transplant recipients with acquired cystic kidney disease. *Clin J Am Soc Nephrol* 2007; 2: 750–756
14. Newstead CG. Cancer risk in patients on dialysis. *Lancet* 1999; 354: 90–91
15. Tang H, Ng JHK. Googling for a diagnosis—use of Google as a diagnostic aid: internet based study. *Br Med J* 2006; 333: 1143–1145
16. Muir EG, Bell AJY, Barlow KA. Multiple primary carcinomata of the colon, duodenum, and larynx associated with kerato-acanthomata of the face. *Br J Surg* 1967; 54: 191–195
17. Torre D. Multiple sebaceous tumors. *Arch Dermatol* 1968; 98: 549–551
18. Shalin SC, Lyle S, Calonje E, Lazar AJ. Sebaceous neoplasia and the Muir-Torre syndrome: important connections with clinical implications. *Histopathology* 2010; 56: 133–147
19. Cohen PR, Kohn SR, Kurzrock R. Association of sebaceous gland tumors and internal malignancy: the Muir-Torre syndrome. *Am J Med* 1991; 90: 606–613
20. Kacerovska D, Cerna K, Martinek P et al. MSH6 mutation in a family affected by Muir-Torre syndrome. *Am J Dermatopathol* 2012; 34: 648–652
21. Vasen HF, Blanco I, Akton-Collan K et al. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. *Gut* 2013; 62: 812–823
22. South CD, Hampel H, Comeras J, Westman JA, Frankel WL, de la Chapelle A. The frequency of Muir-Torre syndrome among Lynch syndrome families. *J Natl Cancer Inst* 2008; 100: 277–281
23. Hall NR, Williams MA, Murday VA, Newton JA, Bishop DT. Muir-Torre syndrome: a variant of the cancer family syndrome. *J Med Genet* 1994; 31: 627–631
24. Dores GM, Curtis RE, Toro JR, Devesa SS, Fraumeni JF Jr. Incidence of cutaneous sebaceous carcinoma and risk of associated neoplasms: insight into Muir-Torre syndrome. *Cancer* 2008; 113: 3372–3381
25. Dowd MB, Kumar RJ, Sharma R, Murali R. Diagnosis and management of sebaceous carcinoma: an Australian experience. *ANZ J Surg* 2008; 78: 158–163
26. Buitrago W, Joseph AK. Sebaceous carcinoma: the great masquerader. *Dermatol Ther* 2008; 21: 459–466
27. Graefe T, Wollina U, Schulz H, Burgdorf W. Muir-Torre syndrome—treatment with isotretinoin and interferon alpha-2a can prevent tumour development. *Dermatology* 2000; 200: 331–333
28. Levi Z, Hazazi R, Kedar-Barnes I et al. Switching from tacrolimus to sirolimus halts the appearance of new sebaceous neoplasms in Muir-Torre syndrome. *Am J Transpl* 2007; 7: 476–479
29. Kominska EC, Jyengar V, Tsoukas M, Shea CR. Borderline sebaceous neoplasm in a renal transplant patient without Muir-Torre syndrome. *J Cutan Pathol* 2012 November 23. doi: 10.1111/j.1600-0425.2012.01862.x [Epub ahead of print]
30. Plocharczyk EF, Frankel WL, Hampel H, Peters SB. Mismatch repair protein deficiency is common in sebaceous neoplasms and suggests the importance of screening for Lynch syndrome. *Am J Dermatopathol* 2013; 35: 191–195

Received for publication: 11.5.13; Accepted in revised form: 13.5.13