A rare case of primary ulcerated amelanotic nodular malignant melanoma in the diabetic foot

Katie Gray, Saul Hill and Sarah Jane Hayhurst

An 81-year-old male with type 2 diabetes mellitus was admitted to hospital following a cardiac arrest. He was the primary informal carer for his wife who suffered from dementia. His medical history was sparse, suggesting he did not access regular medical care. Upon admission, his physical assessment revealed a large ulcerated fungating mass on his left foot for which he was referred to the multidisciplinary diabetic foot team who advised urgent surgical biopsy. The patient reported self-treating the lesion with a razor blade, believing it to be a corn, and had not accessed medical or podiatric care in the community. Following a series of investigations, the patient was diagnosed with aggressive stage IV malignant melanoma due to a rare, primary ulcerated, amelanotic nodular malignant melanoma of his left foot with secondary metastases in the lungs, liver and stomach. Although his cardiac condition was stable, due to his functional decline combined with the invasive nature of his cancer, his treatment plan consisted of palliative care in a specialist unit. Over the next 18 days, he deteriorated rapidly and passed away due to his cancer. Malignant melanoma is the most lethal form of skin tumour, responsible for 79% of skin cancer deaths. The nodular subtype is an invasive and aggressive tumour, which often ulcerates. Malignant melanoma are frequently misdiagnosed as diabetic foot ulcers and, therefore, clinicians should have a high degree of suspicion when managing atypical lesions. Clinicians should consider early specialist dermatological input and biopsy of a non-healing diabetic foot ulcer in the presence of adequate offloading and patent arterial supply and the absence of infection or in those with atypical features. This case study highlights the vulnerable nature of elderly informal carers who may present late for medical treatment and shows the fatal consequences of a late-presenting malignant melanoma.

This article describes a case of a large, primary ulcerated, amelanotic nodular malignant melanoma of the foot with multiple secondary metastatic lesions, which was found incidentally following emergency admission for cardiac arrest in a patient with type 2 diabetes mellitus (T2DM). This article highlights the importance of early detection of malignant melanoma of the foot and the vulnerable nature of informal elderly carers.

Case study

The patient was an 81-year-old male with a past significant medical history of diet-controlled T2DM, stage-3 chronic kidney disease, hypertension and hyperlipidaemia. He had signs of peripheral neuropathy with diminished protective sensation, but no evidence of peripheral arterial disease. Details of previous HbA_{1c} measurements, and other medical data associated with his T2DM, were sparse, suggesting that he did not access regular medical care. In 2010, his HbA_{1c} was 41 mmol/mol, while in 2018, it was 34 mmol/mol. His medication consisted of Ramipril and Atorvastatin. He had a long history

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Article points

1. Cardiovascular disease, diabetes mellitus and cancer are often diagnosed in the same individual.
2. Malignant melanomas are frequently misdiagnosed as diabetic foot ulcers and therefore clinicians should have a high degree of suspicion when managing atypical lesions.
3. Clinicians should consider biopsy of a non-healing diabetic foot ulcer in the presence of adequate offloading and patent arterial supply and the absence of infection.

Key words

- Diabetic foot
- Elderly carer
- Malignant melanoma

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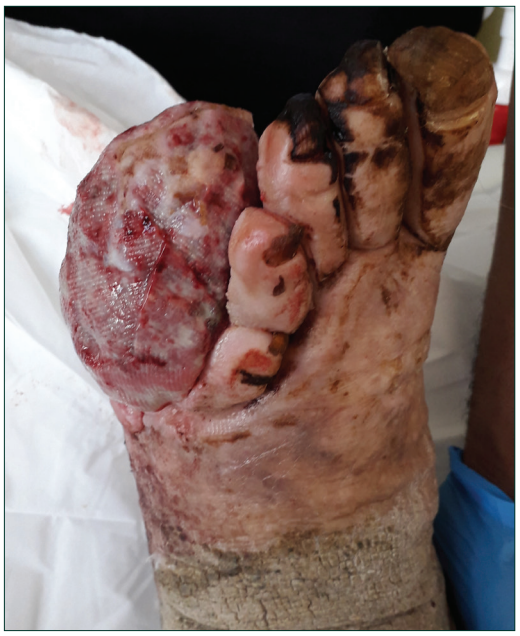


Figure 1 (left). Malignant melanoma upon initial presentation to the multidisciplinary foot team.

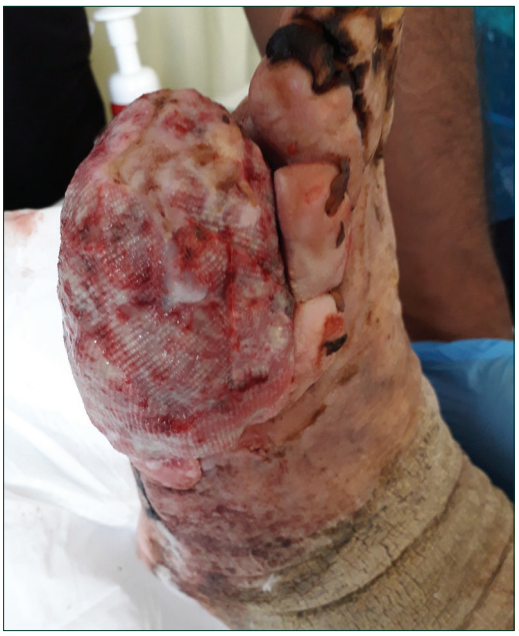


Figure 2 (right). Note the thickness and the amelanotic ulcerated appearance of the malignant melanoma.

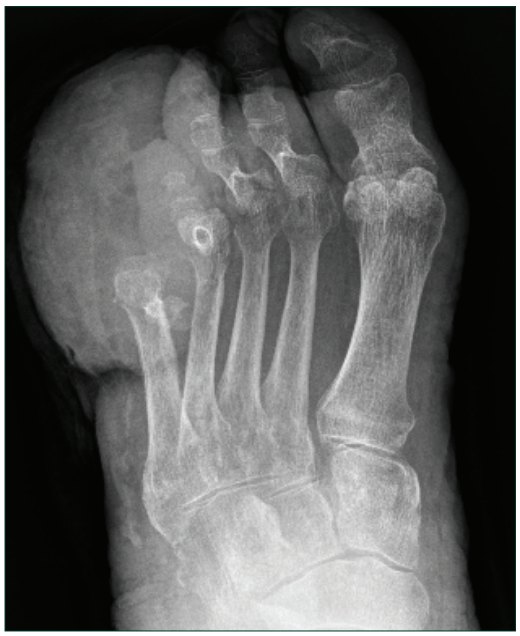


Figure 3 (left). Plain radiograph, dorsoplantar view of left foot showing the soft tissue mass.

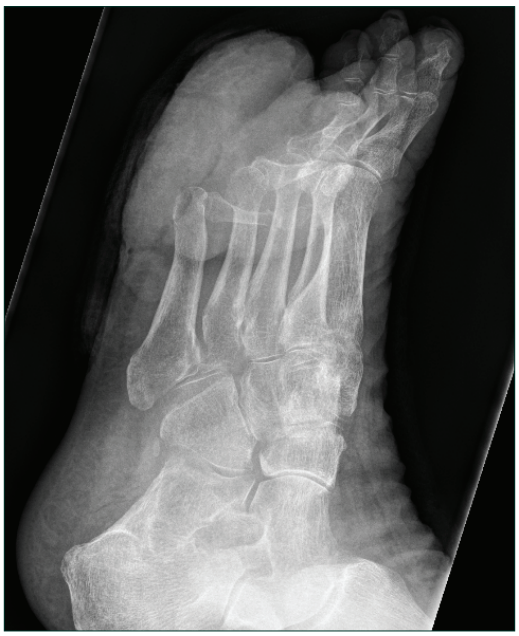


Figure 4 (right). Plain radiograph, medial-oblique view shows hyperextension with dislocation of the fifth toe due to the soft tissue mass.

of smoking and was a primary informal carer for his wife who suffered from dementia.

This gentleman collapsed at home following a cardiac arrest and received successful on-site resuscitation by paramedics who subsequently admitted him to hospital through the Accident and Emergency Department. He was diagnosed with an inferoposterior ST-elevation myocardial infarction. Following medical stabilisation, a physical examination revealed a large malodourous fungating exophytic mass on his left foot, inferior to and extending distally from the plantar aspect of his third, fourth and fifth toes, composed of amelanotic hypergranulating tissue (*Figures 1 and 2*). There was no inguinal or axillary lymphadenopathy. The patient reported that the mass had grown rapidly over 4 months and that he had initially self-treated with a razor blade, suspecting it to be a corn. He was not known to the local Foot Protection Team and had not previously accessed any podiatry services. Clinically, the mass appeared ulcerated with

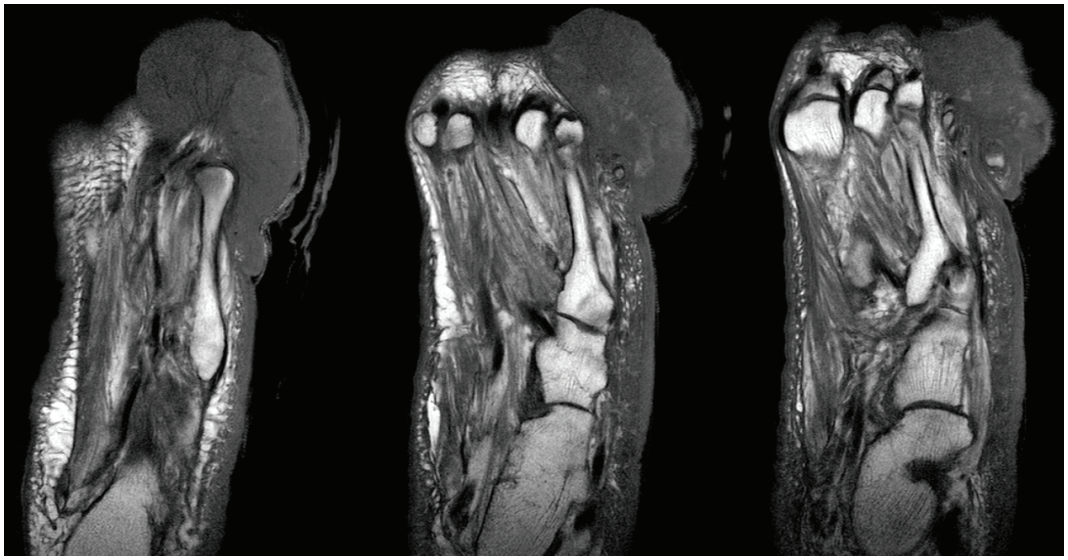
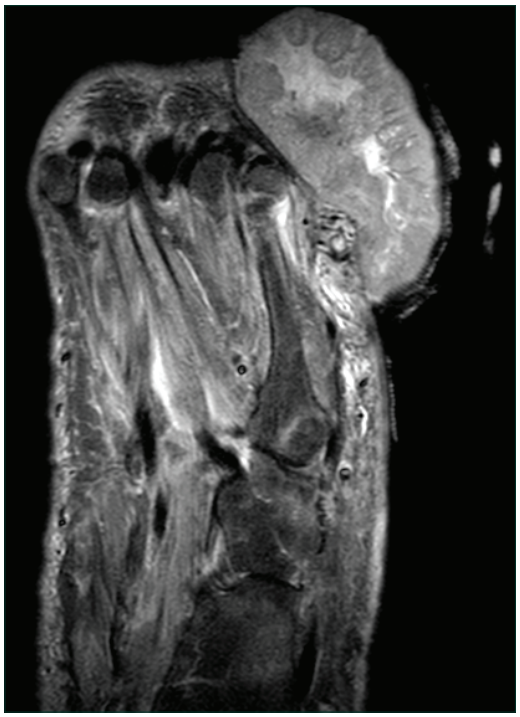


Figure 5. A T1-weighted MRI scan noted that the lesion was predominantly superficial, tracking superficial to the subcutaneous fat in continuity with the dermis, except at the most lateral aspect of the foot where it extended through the subcutaneous fat abutting the head of the fifth metatarsal.



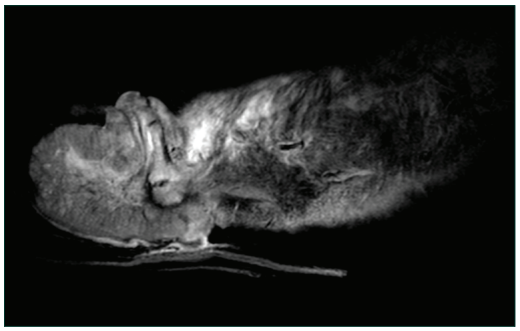


Figure 6. (left) STIR MRI showing bone marrow oedema at the distal shaft of the fifth metatarsal and the adjacent soft tissue mass.

Figure 7. (left) STIR MRI of soft tissue mass.

occasional bleeding and clear serous discharge. The patient reported no significant pain or neurological symptoms. Prior to his cardiac arrest, the patient reported no anorexia, fatigue or weight loss.

The initial treatment plan involved a referral to the multidisciplinary diabetic foot team (MDFT) in line with local guidelines. On initial assessment, the MDFT suggested that the aetiology of the weeping mass was unlikely to be related to his T2DM and advised an urgent surgical referral for biopsy. Accommodative footwear was provided in the form of a post-op shoe to allow the patient to mobilise during his admission.

Plain radiographs of the left foot showed a large soft tissue mass inferior to, and extending distally and laterally, to the third, fourth and fifth metatarsophalangeal joints with resulting extension and hyper-extension of the fourth and fifth toes, respectively *(Figure 3 and 4)*. No osseous involvement was noted.

Magnetic resonance imaging (MRI) showed that the lesion was predominantly superficial, tracking superficial to the subcutaneous fat (*Figure 5*). Short TI Inversion Recovery (STIR) images identified moderate bone marrow oedema to the distal shaft of the fifth metatarsal, but no evidence of cortical breach (*Figures 6 and 7*). The lesion

measured 8.5cm x 4.5cm x 5cm and demonstrated heterogeneous signal. Apart from positional abnormalities of the toes due to the size of the lesion, the remaining osseous structures and intrinsic muscles appeared normal. From this imaging, it was concluded that the soft tissue lesion had an aggressive appearance consistent with either a primary or metastatic tumour.

A liver ultrasound and a pelvis-abdomen-chest computerised tomography scan identified further lesions in the liver, lungs and stomach, in keeping with metastatic neoplasms. Microbiological investigation of the lesion in the form of swabs showed mixed bacterial growth in keeping with commensals. A core biopsy of the lesion was sent for both histopathology and immunohistochemistry, and revealed that the mass was an ulcerated amelanotic malignant melanoma with estimated tumour content of 90% with nodular features.

This patient was diagnosed with stage IV malignant melanoma due to a primary ulcerated amelanotic nodular malignant melanoma of his left foot with secondary metastases in the lungs, liver and stomach. Although his cardiac condition was stable, due to his functional decline combined with the invasive nature of his cancer, his treatment plan consisted of palliative care in a specialist unit. Sadly, he passed away 18 days later due to the cancer.

Discussion

Cardiovascular disease, diabetes mellitus and cancer

Cardiovascular disease, diabetes mellitus (DM) and cancer are leading causes of morbidity and mortality worldwide, the incidence of which is increasing at an alarming rate (GBD 2016 Causes of Death Collaborators, 2017). This triad of diseases is responsible for more than 25 million deaths globally each year and has a severe adverse effect on the health economy (Chun-Song et al, 2014). DM and cancer are frequently encountered and complex pathologies with all subtypes having a dramatic impact on a patient's quality of life (Giovannucci et al, 2010). Furthermore, in those with DM, cardiovascular disease is the leading cause of death, while in cancer survivors it is the second leading cause after secondary malignancies (Daher et al, 2012; Leon and Maddox, 2015).

The incidence of cardiovascular disease, DM and cancer is known to increase with age and this triad if often diagnosed in the same individual (Giovannucci et al, 2010; Koene et al, 2016). However, even when adjusting for age, the frequency of DM and cancer occurring in the same individual is significantly higher than one would expect (Giovannucci et al, 2010). Recent epidemiological studies demonstrate that several forms of cancer, including pancreas, liver, colorectal, urinary tract and breast, occur more frequently in individuals with T2DM and have higher mortality rates (Vigneri et al, 2009).

Cardiovascular disease, DM and cancer share many anthropometric, environmental and social risk factors, several of which are modifiable (Giovannucci et al, 2010; Koene et al, 2016). Non-modifiable risk factors include age, male gender and social deprivation, while modifiable risk factors include obesity, diet, physical activity and tobacco smoking. Although metabolic and hormonal disturbances may play a role, emerging evidence suggests the presence of biological links between cancer and T2DM (Giovannucci et al, 2010). Lee and Chan (2015) recently suggested that DNA mutation is a common characteristic in carcinogenesis and that individuals with T2DM produce a higher level of reactive oxygen species and have lower levels of antioxidant capacity with consequent higher levels of DNA damage. This can lead to a number of different forms of mutation, resulting in aberrant cells and the development of cancer.

Malignant melanoma

A malignant tumour of melanocytes, malignant melanoma, is the most lethal form of skin tumour responsible for 79% of skin cancer deaths (Kong et al, 2005; Gawkrodger and Ardern-Jones, 2017). The third most common skin cancer in the United Kingdom, malignant melanoma accounted for 13,348 new cases and 2,209 deaths in 2011 (National Institute for Health and Care Excellence [NICE], 2018). Malignant melanoma is responsible for more deaths than all other skin cancers combined with the greatest burden falling on the elderly and male gender in the European, North American, and Australasian populations (Karimkhani et al, 2017; NICE, 2018). One in 10 of those affected with malignant melanoma will develop lung metastases during the course of their disease, while 54–77% will develop hepatic metastases (Damsky et al, 2010).

For patients with stage IV melanoma, due to the distant metastases, the prognosis is generally

very poor with historical 5-year survival rates of less than 10% (Dickson and Gershenwald, 2011). A meta-analysis of cohort studies by Qi et al (2014) suggested that T2DM is an independent risk factor for malignant melanoma with a pooled relative risk of 1.15 (95% CI, 1.00–1.32) in DM compared with non-DM. Hui-Wen et al (2016) in a retrospective cohort study reported that the risk of developing skin cancer was significantly higher in older adults (≥60 years) with DM and that males and those with coronary artery disease were at the highest risk.

Four subtypes of primary cutaneous malignant melanoma are recognised based on clinical and pathological criteria: nodular, superficial spreading, lentigo and acral lentiginous (Hikawa et al, 2014). A fifth subtype, polypoid, has recently been suggested in the literature (Hikawa et al, 2014). Malignant melanomas that produce little or no pigment are termed amelanotic melanomas (Khishfe et al, 2014). Nodular malignant melanoma is an invasive and aggressive tumour with a male preponderance noted for its rapid growth and advanced thickness at presentation and is often associated with breakdown of the overlying epidermis and ulceration (Khishfe et al, 2014; Gawkrodger and Ardern-Jones, 2017).

The primary site of malignant melanoma is known to vary according to race. In Caucasians, the head, neck, trunk and lower-extremity region is frequently affected, while the hands and feet are common sites in non-Caucasians (East Asians, Africans and indigenous inhabitant of the Americas) (Nam et al, 2016). Nam et al (2016) reviewed 52 cases of malignant melanoma of the foot and found that 86.6% and 13.4% were of the subtypes acral lentiginous and nodular, respectively, with 42.3%, 26.9%, 21.1%, 7.7% and 1.9% occurring on the heel, mid-sole, toes, lateral boarder and medial boarder of the foot, respectively.

Malignant melanoma are commonly misdiagnosed occurring in approximately 40% of all cases (Metzger et al, 1998). Metzger et al (1998) reported that a misdiagnosis, on average, delays treatment for 12 months and is associated with increased tumour thickness, advanced staging, and lower 5-year survival rates. Common misdiagnoses include verrucae, fungal infections, foot ulcers and hyperkeratotic lesions (Fortin et al, 1995). Furthermore, lesions on the plantar aspect of the foot often go unnoticed by both patients and clinicians. Plantar and subungual malignant melanomas often do not fit the 'changing mole' pattern and, therefore, non-specialists clinicians frequently misdiagnose, necessitating the importance of early referral to a dermatologist (Metzger et al, 1998).

Table 1. Weighted 7-point checklist for suspected malignant melanoma (NICE, 2018).

Major features of the lesion (scoring 2 points each): - Change in size - Irregular shape - Irregular colour
Minor features of the lesion (scoring 1 point each): - Largest diameter 7 mm or more - Inflammation - Oozing or exudate - Change in sensation
A score of 3 or more warrants urgent referral for review within 2 weeks.

It is not uncommon for malignant melanoma of the foot in someone with DM to be misdiagnosed as a diabetic foot ulcer, particularly if the lesion is small, ulcerated and amelanotic (Gao et al, 2017). There is currently no guidance on when to refer a static non-healing diabetic foot ulcer to a specialist dermatologist for a second opinion. Therefore, the authors' recommend that clinicians should consider early specialist dermatological input and biopsy of a non-healing diabetic foot ulcer in the presence of adequate offloading and patent arterial supply and the absence of infection or those with atypical features.

Current NICE (2018) guidance suggests that those suspected of having a malignant melanoma are referred using the suspected cancer referral pathway for an appointment within 2 weeks if they have a suspicious skin lesion with a weighted seven-point checklist score of three or more (*Table 1*). With tumour thickness an important survival prognosticator for malignant melanoma, it is not surprising that the two commonly used classifications systems, Clark's level of anatomic invasion (*Table 2*) and Breslow's tumour thickness (*Table 3*), demonstrate a poorer outcome with higher levels (Roy, 2011). Malignant melanoma

Table 2. Clark's level of invasion with 5-year survival (Roy, 2011).

Level	Description	5-year survival rate
I	Involvement of epidermis only	100%
II	Papillary dermis involvement	90-100%
III	The junction of the papillary dermis and reticular dermis is involved	80-90%
IV	Tumour extends to reticular dermis	60-70%
V	Subcutaneous fat is involved	<30%

Table 3. Breslow's staging for tumour thickness (Roy, 2011).

Stage	Thickness
I	0.75 mm or less
II	0.76 – 1.49 mm
III	1.50 – 2.49 mm
IV	2.50 – 3.99 mm
V	4.00 – 7.99 mm

of the foot poses a particular challenge for early diagnosis due to its location at the end of anatomic peninsular, which only becomes more isolated with advancing age as mobility and visual acuity decreases.

Elderly carers

Over the next 20-years, it is expected that the elderly population (≥75-years old) will double (Thomas et al, 2015). It is currently thought that the average 75-year old patient has three medical disorders, while 25% also have a functional disability significant enough to require carer assistance (Thomas et al, 2015). Ill health and frailty contribute to this population's vulnerability and isolation. As the elderly population grows, so does the number of informal carers. Informal carers are usually spouses and family members who have been thrust into the position of carer through the ailing health of a loved one. Evidence shows that informal carers experience poorer physical and mental health than the general population and often neglect their own health needs (Thomas et al, 2015).

Conclusion

Cardiovascular disease, DM and cancer are a triad of diseases often found in the same individual. This case study highlights the vulnerable nature of elderly informal carers and shows the fatal consequences of a late-presenting malignant melanoma. Furthermore, it demonstrates that these patients may be referred to the MDFT for review. Although a few cases are reported in the literature to the authors' knowledge, the severity and nature of the lesion is not commonly seen by MDFT, particularly at this terminal stage.

It is difficult to determine what the outcome for this patient would have been had they had access to a Foot Protection Team or Community Podiatry Service earlier on. However, one could assume a higher survival rate with earlier diagnosis. This article contributes to the knowledge base of the diabetic foot with metastatic tumour to ensure future clinical presentations are detected rapidly by MDFT. This article highlights the importance of early diagnosis in malignant melanoma in the diabetic foot and that a high degree of suspicion should be present when dealing with atypical lesions. ■

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Chun-Song H, Qing-Hua W, Da-Yi H (2014) Cardiovascular, diabetes, and cancer strips: evidences, mechanisms, and classifications. *J Thorac Dis* 6(9): 1319–28

Daher IN, Daigle TR, Bhatia N et al (2012) The Prevention of Cardiovascular Disease in Cancer Survivors. *Tex Heart Inst J* 39(2): 190–8

Damsky WE, Rosenbaum LE, Bosenberg M (2010) Decoding melanoma metastasis. *Cancers (Basel)* 3(1): 126–63
Dickson PV, Gershenwald JE (2011) Staging and prognosis of cutaneous melanoma. *Surg Oncol Clin N Am* 20(1): 1–17
Fortin PT, Freiberg AA, Rees R et al (1995) Malignant melanoma of the foot and ankle. *J Bone Joint Surg Am* 77(9): 1396–403
Gao W, Chen D, Ran X (2017) Malignant melanoma misdiagnosed as diabetic foot ulcer: a case report. *Medicine (Baltimore)* 96(29): e7541
Gawkrodger DJ, Ardern-Jones MR. (2017) Dermatology: An Illustrated colour text. Elsevier, London: pp96–7
GBD 2016 Causes of Death Collaborators (2017) Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet* 390(10100): 1151–210
Giovannucci E, Harlan DM, Archer MC et al (2010) Diabetes and cancer: a consensus report. *Diabetes Care* 33(7): 1674–85
Hikawa RS, Kanehisa ES, Enokihara M et al (2014) Polypoid melanoma and superficial spreading melanoma different subtypes in the same lesion. *An Bras Dermatol* 89(4): 666–8
Hui-Wen T, Yow-Ling S, Kuo-Wang T et al (2016) Risk of skin cancer in patients with diabetes mellitus: a nationwide retrospective cohort study in Taiwan. *Medicine* 95(26): 1–11
Karimkhani C, Green AC, Nijsten T et al (2017) The global burden of melanoma: results from the Global Burden of Disease Study 2015. *Br J Dermatol* 177(1): 134–40
Khishfe BF, Krass LM, Nasr I (2014) Case report: Lower extremity amelanotic nodular melanoma. *Austin Journal of Emergency and Critical Care Medicine* 1(2): 1-3
Koene RJ, Prizment AE, Blaes A et al (2016) Shared risk factors in cardiovascular disease and cancer. *Circulation* 133(11): 1104–14
Kong MF, Jogia R, Srinivasan BT, Jackson S (2005) Malignant melanoma presenting as foot ulcer. *Diabet Med* 22(7): 956–7
Lee SC, Chan JCN (2015) Evidence for DNA damage as a biological link between diabetes and cancer. *Chin Med J (Engl)* 128(1): 1543–8
Leon BM, Maddox TM (2015) Diabetes and cardiovascular disease: epidemiology, biological mechanisms, treatment recommendations and future research. *World J Diabetes* 6(13): 1246–58
Metzger S, Ellwanger U, Stroebel W et al (1998) Extent and consequences of physician delay in the diagnosis of acral melanoma. *Melanoma Res* 8(2): 181–6
Nam KW, Bae YC, Nam SB (2016) Characteristic and treatment of cutaneous melanoma of the foot. *Arch Plast Surg* 43(1): 59–65
NICE (2018) *Melanoma: Assessment and Management* (NG 14). Available at: https://bit.ly/2OcHl5m (accessed 26.09.2018)
Qi L, Qi X, Xiong H et al (2014) Type 2 diabetes mellitus and risk of malignant melanoma: a systematic review and meta-analysis of cohort studies. *Iran J Public Health* 43(7): 857–66
Roy H (2011) *Short Textbook of Surgery with Focus on Clinical Skills*. Jaypee, London: pp82–90
Thomas GPA, Saunders CL, Roland MO et al (2015) Informal carers' health-related quality of life and patient experience in primary care: evidence from 195,364 carers in England responding to a national survey. *BMC Fam Pract* 16: 62
Vigneri P, Frasca F, Sciacca L et al (2009) Diabetes and cancer. *Endocr Relat Cancer* 16(4): 1103–23