Endocrinology, Diabetes & Metabolism CASE REPORTS

A Mantovani and others | Primary cutaneous B-cell lymphoma and T2DM

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Primary cutaneous B-cell lymphoma and chronic leg ulcers in a patient with type 2 diabetes

Alessandro Mantovani[1], Fabrizia Perrone[1], Vincenzo Stoico[1], Isabella Pichiri[1], Laura Salvotelli[1], Ilaria Teobaldi[1], Massimiliano Bruti[2], Michela Conti[3], Luca Cima[4], Albino Eccher[4] and Enzo Bonora[1]

[1]Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, [2]Division of Plastic Surgery, Department of Surgery, [3]Division of Infectious Disease, Department of Medicine and [4]Division of Pathology Unit, Department of Diagnostics and Public Health, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy

Correspondence should be addressed to A Mantovani
Email
alessandro.mantovani24@gmail.com

Summary

The incidences of type 2 diabetes mellitus and many cancers are rapidly increasing worldwide. Diabetes is a strong risk factor for some cancers (including lymphomas) and is also associated with adverse cancer outcomes. After gastrointestinal tract, the skin is the second most frequent extranodal site involved by non-Hodgkin lymphomas and the cutaneous B-cell lymphomas (CBCLs) range from 25% to 30% of all primary cutaneous lymphomas. The primary cutaneous diffuse large B-cell lymphoma (PCDLBCL) is an aggressive lymphoma with a poor prognosis, representing roughly 20% of all primary CBCLs. Classically, the cutaneous manifestation of this lymphoma is a red or violaceous tumors arising on a leg. To date, despite the large body of evidence suggesting that diabetes is strongly associated with an increased risk of some cancers, very little information is available regarding a possible association between type 2 diabetes and primary cutaneous diffuse large B-cell lymphoma. In this report, we will present the case of a white adult patient with type 2 diabetes with chronic leg ulcers complicated by a primary cutaneous diffuse large B-cell lymphoma.

Learning points:

- Diabetes mellitus is increasing worldwide as well as the incidence of many cancers.
- Diabetes mellitus is a powerful risk factor for some cancers (including lymphomas) and is strongly associated with adverse cancer outcomes.
- Seen that diabetes is strongly associated with an increased risk of cancers (including cutaneous lymphomas), clinicians should always keep in mind this complication in elderly patients with type 2 diabetes, even in a chronic leg ulcer with hypertrophy of the wound edge, which is hard to heal and does not have the typical characteristics of a diabetic or vascular ulcer. In these cases, a biopsy should be performed to rule out a neoplasm.
- Early diagnosis and correct management of cancer in a patient with type 2 diabetes are crucial to improve clinical outcomes.

Background

In 2014, the total prevalence of type 2 diabetes (T2DM) was calculated to be 9% of the adult population (roughly 415 million individuals) (1). However, it is estimated that the total prevalence of diabetes mellitus will increase to nearly 600 million in 2035 and that approximately 80% of these individuals will live in developing countries (1).

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In addition to the excess risk of vascular and infectious disease, recent data strongly suggest that patients with T2DM had a two-fold increased risk of dying from cancer, including lymphomas, compared to those without diabetes (2, 3).

The skin is the second most frequent extranodal site associated with non-Hodgkin lymphomas, after the gastrointestinal tract (4). Classically, the identification of a primary cutaneous lymphoma necessitates that there is no extracutaneous disease involved at the moment of the diagnosis (4). Although the cutaneous T-cell lymphomas (CTCLs) are the more common subtype, the cutaneous B-cell lymphomas (CBCLs) range from 25% to 30% of all primary cutaneous lymphomas (5, 6, 7). To note, the primary cutaneous diffuse large B-cell lymphoma (PCDLBCL), leg type, is a rare and aggressive lymphoma, which represents approximately 4% of all cutaneous lymphomas and 20% of all primary CBCLs (5, 6, 7). PCDLBCL often affects elderly individuals and females seem to be more affected than male (5, 6, 7). Traditionally, the cutaneous manifestation of this lymphoma is a red or violaceous tumors that becomes apparent on a leg (4). At present, although there are many data regarding the impact of diabetes on the risk of some cancers, very little information is available on a possible association between T2DM and PCDLBCL. In this report, we will present the case of a white adult patient with T2DM with chronic leg ulcers complicated by a PCDLBCL.

Case presentation

An 81-year-old white male patient with T2DM was admitted to our department for the worsening of the two ulcerative left lower limb injuries. The diagnosis of T2DM was made approximately 20 years ago and a treatment with insulin (lispro plus glargine) was initiated in 2009 with a moderate glycemic compensation. In addition to T2DM, his medical history included: hypertension, obesity, chronic kidney disease (stage IIIa), peripheral arteriopathy, ischemic heart disease and a newly-diagnosed hepatic nodule compatible with a well-differentiated hepatocellular carcinoma. To note, the patients was not a smoker. The ulcerative left lower limb injuries appeared three months ago. They had been treated with a conservative approach by dressings with topical antiseptic and oral antibiotic therapy with ciprofloxacin plus amoxicillin-clavulanate, according to Klebsiella pneumoniae multi-drug resistant and Acinetobacter baumanii isolated by biopsy performed in an ambulatory setting. Notably and interestingly, in the last month, there has been an increase of the hypertrophy of the wound edge. On admission, the patient was afebrile, but had pain in the left leg. The larger leg chronic ulcer had a size of 84 × 50 mm, while the smaller one had a size of 36 × 16 mm. Both ulcers appeared infected, malodorous, very erythematous with net and hypertrophic margins (Fig. 1). Another similar lesion was found in the dorsal part of the left ankle. Given the previous microbiological examination, the patient was placed in contact isolation.

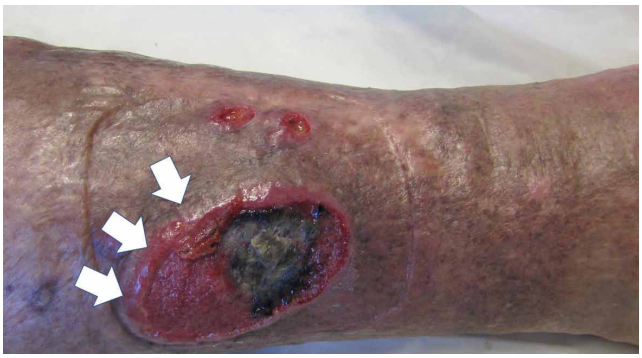

Figure 1
Clinical aspect of the larger leg ulcer at presentation. The net and hypertrophic margins of the injury are indicated by arrows.

Investigation

At admission, blood tests revealed: white blood cells (WBC) 5.1×10^9/L (normal range: 4.3–10), hemoglobin 104 g/L (normal range: 135–170), platelets 125 × 100 000/mm^3 (normal range: 150–450), fasting plasma glucose 6.4 mmol/L (normal range: 3.5–5.5), A1c 42 mmol/mol (normal range: <36), alanine aminotransferase (ALT) 42 U/L (normal range: 6–50), gamma-glutamyl transpeptidase (GGT) 107 U/L (normal range: 4–60), creatinine 70 µmol/L (normal range: 53–115), C-reactive protein (CRP) 17 mg/L (normal range <5) and procalcitonin (PCT) 0.04 ng/mL (normal range <0.05), carcinoembryonic antigen (CEA) 1.9 µg/L (normal range <4.0), carbohydrate antigen (CA) 19–94 KU/L (normal range <35) and alpha-feto protein (AFP) <1 KU/L (normal range <10). We performed a new biopsy of the soft tissue at the level of the larger leg ulcer, that confirmed the presence of Klebsiella pneumoniae and Acinetobacter baumannii, but also revealed the presence of Staphylococcus aureus methicillin-resistant. After the infectious disease counseling, we started a systemic antibiotic therapy with carbapenem *plus* tigecycline at high dosages. The radiograph of the left leg excluded the presence of underlying osteomyelitis, but the radiologist reported the presence of some coarse nodules in the lower third of the left leg. Regular medications in combination with targeted systemic antibiotic therapy contributed

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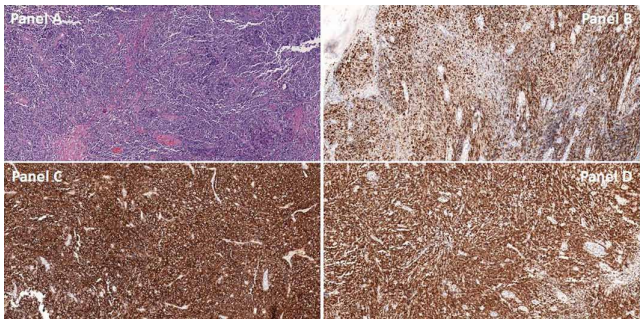

Figure 2
Incisional biopsy of the leg ulcer. Panel A: Histological findings of a primary cutaneous diffuse large B-cell lymphoma, leg type. Panel B: Immunohistochemical analysis of *Ki67* shows a high cell proliferation (>90%). Panel C: Immunohistochemical analysis of *CD20*. Panel D: Immunohistochemical analysis of *Bcl-2*.

to the reduction of inflammatory markers (CRP 5 mg/L) and the improvement of the inflammatory component of the ulcers. However, the unusual appearance of the ulcers as well as the detection of coarse nodulation on radiography imposed the execution of an incisional biopsy with subsequent histological examination that revealed an infiltrate of monomorphic large cells in the dermis with prominent nucleoli and frequent mitoses. The immunohistochemical analysis showed a diffuse expression of *CD20*, *BCL-2*, *BCL-6* and *MUM-1* as well as a high proliferative index (*Ki67* >90%) (Fig. 2, Panel A, B, C and D). The final diagnosis was a PCDLBCL, 'leg type', according to World Health Organization (WHO) Lymphoma Classification (7). Subsequently, we performed a total-body CT that confirmed the presence of the hepatic nodule and excluded other extracutaneous disease.

Treatment, outcome and follow-up

The clinical case was extensively discussed with hematologist and radiotherapist, who suggested only a localized electron beam radiotherapy. The cycles of radiotherapy still in progress have allowed an improvement of the lesion. In addition, the antibiotic therapy was continued for other 3 weeks. The subsequent microbiological tests were negative. After discharge, a positron emission tomography (PET) scan was performed showing the presence of numerous hypermetabolic lymph nodes in the left groin and at the level of the ipsilateral external and common iliac artery. In addition, the spleen was hypermetabolic and increased in volume. Collectively, these findings strongly suggest a progression of disease.

Discussion

The incidences of T2DM and cancers are rapidly increasing worldwide (1). In 2012, the number of deaths ascribed to cancer was estimated to have exceeded 8 million and the incidence rates of some cancers, including breast cancer, lung cancer, prostate cancer and non-Hodgkin lymphomas, are expected to raise in the future (2). Over the last 50 years, mounting evidence has clearly documented that there is a strong and independent association between diabetes and some cancers, including lymphomas (2). For example, in a community-based cohort study involving 820 900 individuals, Seshasai *et al.* have reported that diabetes was strongly associated with substantial premature death from several cancers, independent of many important risk factors and potential confounders (8). More recently, in a small observational study including 144 patients with cutaneous T-cell lymphomas at Helsinki University Central Hospital, Väkevä *et al.* have documented that the prevalence of T2DM was significantly increased among patients with cutaneous T-cell lymphomas (without a relationship with obesity) compared with an age-standardized control population (9).

As known, after gastrointestinal tract, the skin is the second most frequent extranodal site implied by non-Hodgkin lymphomas (4). Generally, the cutaneous T-cell lymphomas are more common than cutaneous B-cell lymphomas, which are a quarter of all primary cutaneous lymphomas (5, 6, 7). Notably, the PCDLBCL, also named 'leg type', is an infrequent lymphoma with a poor prognosis (5, 6, 7).

Our patient was an 81-year-old male with T2DM complicated by chronic and infected leg ulcerations. Importantly, the features of leg ulcers were somewhat atypical for a diabetic or vascular injury, in as much as they were red and characterized by net and hypertrophic margins. Given the unusual features of these lesions, the chronicity as well as the persistence of infection (despite a targeted oral antibiotic therapy), we performed a histological investigation. To our surprise, we found a PCDLBCL, 'leg type', with a high cell proliferation (Fig. 2, Panel A, B, C and D). The total-body CT excluded the presence of other extracutaneous disease, with the exception of the hepatic nodule, which was already known and was periodically checked by imaging. Thus, a diagnosis of PCDLBCL was formulated. Subsequently, the PET scan showed a progression of disease, confirming the poor outcome.

To date, the physiopathology of PCDLBCL is not completely understood. The cause seems to be multifactorial involving chronic antigen stimulation, such as viral and bacterial infections (4, 5, 6, 7). Obesity and T2DM are strongly associated with insulin resistance and also with a chronic inflammatory state, promoting the release into bloodstream of several molecules, such as interleukin-1 (IL-1), IL-6 and tumor necrosis factor-alpha (TNF-α) (2). When insulin resistance develops, insulin concentrations raise in the blood, resulting in an overproduction of insulin-like growth factor 1 (IGF-1), which can stimulate cellular proliferation, and also inhibit apoptosis (2). There is now convincing evidence to suggest that all these diabetes-related mediators can concur to the development of certain cancers by promoting cellular growth and proliferation, inhibition of cellular apoptosis, angiogenesis and DNA damage (2). Interestingly, emerging experimental studies also suggest that, compared with those without T2DM, patients with T2DM have a higher level of genomic instability as well as several epigenetic alterations that may play a role in the development of cancer (2). Furthermore, our patient has been treated with insulin for a long time. It is important to remember that several glucose-lowering agents (including insulin) are associated with cancer risk (2). In particular, some clinical studies published in 2009 suggested the existence of a significant association between the use of glargine and the increased risk of cancer (2). A potential biological mechanism of this relationship was provided by experimental studies suggesting that glargine may have mitogenic property and increase the activity of the IGF-1 receptor (2). However, these studies have been largely criticized for some methodological limitations, and these results have not been confirmed in other subsequent studies (2, 10).

In conclusion, our case report is clinically relevant as it highlights the finding of a PCDLBCL in a chronic leg ulcer in a patient with T2DM. Seen that diabetes is strongly associated with an increased risk of some cancers (including lymphomas), clinicians should always consider this event in elderly patients with T2DM, even in a chronic ulcer with hypertrophic margins, which is hard to heal and does not have the typical characteristics of a diabetic or vascular ulcer. In these cases, a biopsy should be performed to rule out a neoplasm. Histological differential diagnosis includes epidermal cancers, melanoma, Kaposi's sarcoma and cutaneous B-cell and T-cell lymphomas. Finally, the early diagnosis and management of cancer are crucial to improve clinical outcomes.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Patient consent
Written informed consent has been obtained from the patient for the publication of this report.

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References

1 Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U & Shaw JE 2014 Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Research and Clinical Practice* **103** 137–149. (doi:10.1016/j.diabres.2013.11.002)
2 Klil-Drori AJ, Azoulay L & Pollak MN 2017 Cancer, obesity, diabetes, and antidiabetic drugs: is the fog clearing? *Nature Reviews Clinical Oncology* **14** 85–99. (doi:10.1038/nrclinonc.2016.120)
3 Emerging Risk Factors Collaboration, Di Angelantonio E, Kaptoge S, Wormser D, Willeit P, Butterworth AS, Bansal N, O'Keeffe LM, Gao P, Wood AM, *et al*. 2015 Association of cardiometabolic multimorbidity with mortality. *JAMA* **314** 52–60. (doi:10.1001/jama.2015.7008)
4 Newton R, Ferlay J, Beral V & Devesa SS 1997 The epidemiology of non-Hodgkin's lymphoma: comparison of nodal and extra-nodal sites. *International Journal of Cancer* **72** 923–930. (doi:10.1002/(SICI)1097-0215(19970917)72:6<923::AID-IJC1>3.0.CO;2-R)
5 Bradford PT, Devesa SS, Anderson WF & Toro JR 2009 Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. *Blood* **113** 5064–5073. (doi:10.1182/blood-2008-10-184168)
6 Swerdlow SH, Quintanilla-Martinez L, Willemze R & Kinney MC 2013 Cutaneous B-cell lymphoproliferative disorders: report of the 2011 Society for Hematopathology/European Association for Haematopathology workshop. *American Journal of Clinical Pathology* **139** 515–535. (doi:10.1309/AJCPNLC9NC9WTQYY)
7 Wilcox RA 2013 Cutaneous B-cell lymphomas: 2013 update on diagnosis, risk-stratification, and management. *American Journal of Hematology* **88** 73–76. (doi:10.1002/ajh.23360)
8 Emerging Risk Factors Collaboration, Seshasai SR, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, Whincup PH, Mukamal KJ, Gillum RF, *et al*. 2011 Diabetes mellitus, fasting glucose, and risk of cause-specific death. *New England Journal of Medicine* **364** 829–841. (doi:10.1056/NEJMoa1008862)
9 Väkevä L, Lipsanen T, Sintonen H & Ranki A 2017 Morbidity and causes of death in patients with cutaneous T-cell lymphoma in Finland. *Acta Dermato-Venereologica*. (doi:10.2340/00015555-2629)
10 Wu JW, Filion KB, Azoulay L, Doll MK & Suissa S 2016 The effect of long-acting insulin analogs on the risk of cancer: a systematic review of observational studies. *Diabetes Care* **39** 486–494. (doi:10.2337/dc15-1816)

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