CASE REPORT

The cryptic enemy: Exploring paraneoplastic manifestations of lymphoma through a case of jejunal lymphoma in a renal transplant recipient

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Abstract

Introduction

Lymphoproliferative disorders are commonly associated with paraneoplastic manifestations which might precede the onset of the neoplasm. Therefore, high index of suspicion in at-risk populations can help early detection of the lymphoma.

Case history

A young female presented with anaemia and diarrhoea eighteen months after the kidney transplant and was diagnosed to have stage IV jejunal lymphoma with pelvic skeletal deposits. She had an episode of left sacroiliitis nine-months prior to this. The original renal disease that rapidly progressed to end-stage-kidney failure was membrano-proliferative glomerulonephritis. Current presentation was complicated by possible cardiac autonomic failure.

Discussion and conclusion

Sacroiliitis, glomerulonephritis and cardiac autonomic failure are well known paraneoplastic manifestations of lymphoma. All three can precede lymphoma by years or present simultaneously. While our patient was at risk of post-transplant lymphoproliferative disorders (PTLD), we postulate whether the glomerulonephritis and sacroiliitis could have been paraneoplastic. Malignancy related sacroiliitis can be paraneoplastic or related to skeletal deposits. It can seemingly respond to anti-inflammatory therapy. Thorough evaluation of adult onset glomerulonephritis is required to exclude an underlying malignant aetiology. We highlight the importance of protocol based complete analysis of seemingly benign and unrelated conditions which might help discover underlying sinister aetiologies and thereby help change the natural history of both.

Background

The gastrointestinal tract is the most common extra-nodal site of involvement seen with non-Hodgkin's lymphoma [1]. The immunosuppressive state after organ transplantation predisposes an individual towards lymphoproliferative disorders, which is known as post-transplant lymphoproliferative disorders (PTLD). Certain forms are aggressive and rapidly fatal despite therapy [2]. Lymphomas are associated with a multitude of paraneoplastic syndromes, some of which precede it by years. We present a case of PTLD involving the jejunum which was associated with three possible paraneoplastic manifestations, highlighting the importance of a high index of suspicion when seemingly common conditions behave in unusual ways.

Case history

A 42-year-old Asian female kidney transplant recipient presented in July 2020 with exertional shortness of breath of four-months and diarrhoea of one-month duration. Diarrhoea was watery and was associated with feverishness, night sweats, vague periumbilical pain and intermittent melaena.

She had an episode of transient symmetrical polyarthritis in 2010 which resolved with a short course of analgesic therapy. In 2016 she presented with a rapid deterioration of kidney function and was found to have membrano-proliferative glomerulonephritis on biopsy which progressed to end-stage-kidney-disease despite immuno-suppression. The diagnosis was based on light micro-scopic morphology alone, with no immunofluore-scence, electron-microscopy (EM) or details regarding viral, autoimmune and paraprotein screens being available. She underwent live non-related donor kidney transplant in January 2019 along with basiliximab induction therapy followed by standard immunosuppression with prednisolone, mycophenolate mofetil and tacrolimus. She maintained normal graft function without the need for augmentation of immunosuppression. In September 2019, she presented with left buttock pain and constitutional symptoms, and was treated as for infective sacroiliitis based on imaging (MRI) and elevated C-reactive protein (CRP), with good response to a course of antibiotics (CRP 58mg/dl to <6mg/dl). Peripheral blood culture despite prolonged incubation and tuberculosis screening were negative. Attempted image-guided diagnostic tap of the joint had not been successful.

At current presentation, she was febrile and pale with tachycardia (108/min) and postural hypotension (100/70 to 90/60mmHg). Investigations revealed severe microcytic hypochromic anaemia (haemoglobin-5.0g/dl), neutrophil-leukocytosis (White cells-15.6;Neutrophils-11.4×10^3) and normal platelets (398×10^3) without any abnormal cells in the blood picture. The inflammatory markers, erythrocyte sedimentation rate (130mm/first hour) and CRP (110mg/dl) were high and remained high despite negative septic screen and a course of an empirical broad-spectrum antibiotic. Screening upper and lower gastrointestinal endoscopies were unremarkable. Capsular endoscopy followed by jejunoscopy revealed an abnormal erythe-matous area with active bleeding in the jejunum. Biopsy of the same confirmed a high-grade B cell lymphoma (Figures 1-4). MR enteroclysis and contrast enhanced CT abdomen showing para-aortic nodes, splenomegaly and left pelvic skeletal deposits staging her disease as Ann-Arbor-IV.

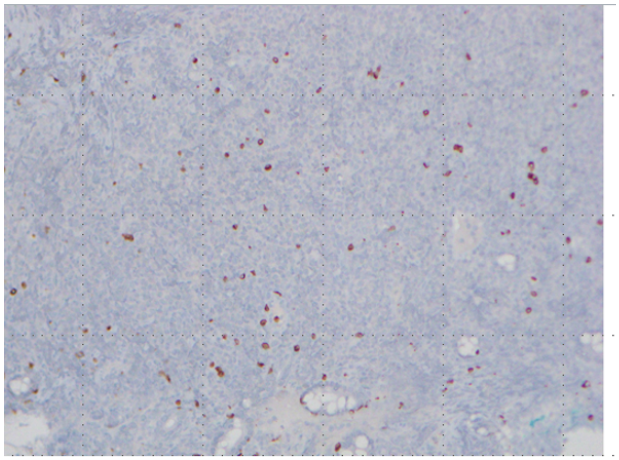

Figure 1. CD 3 stain – A few scattered cells show cytoplasmic positivity.

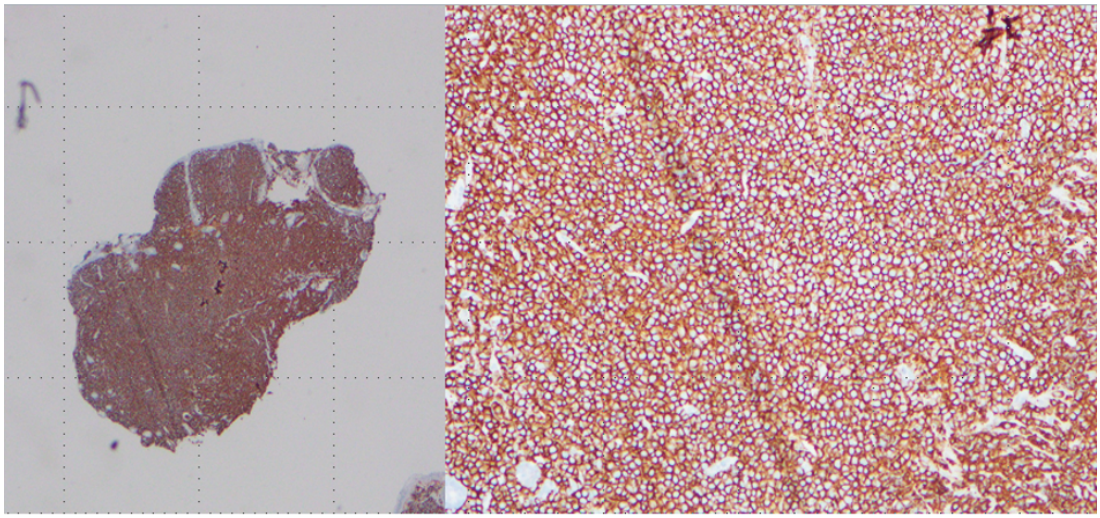

Figure 2. CD 20 stain – The cells in lamina propria show diffuse cytoplasmic strong positivity.

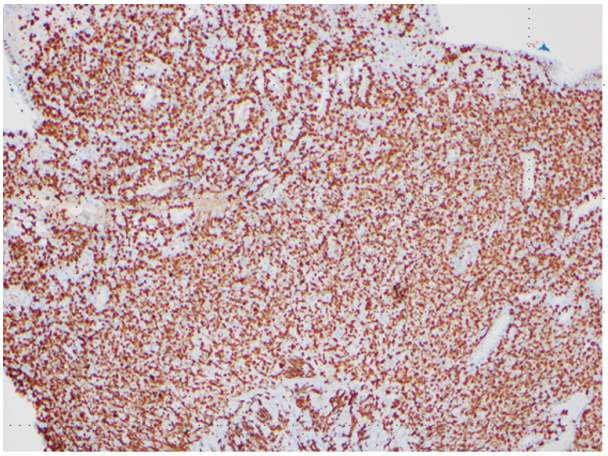

Figure 3. Ki67 stain proliferative index 90%.

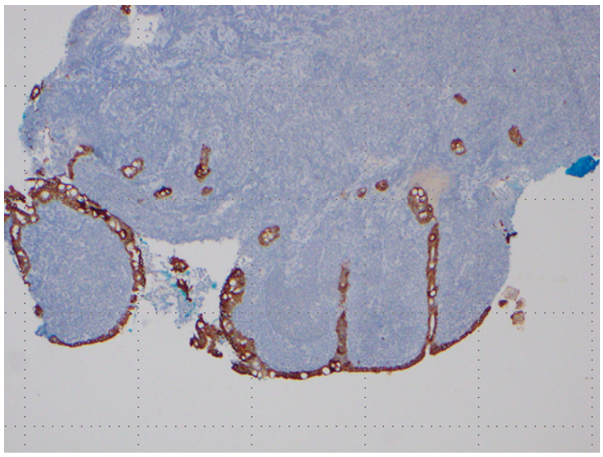

Figure 4. Pan cytokeratin stain AE1/AE2 – Negative in cells in lamina propria. The cells in glandular epithelium is positive.

During the evaluation, she had persistent tachycardia (104-120 beats/minute) and postural dizziness despite correction of anaemia (Hb corrected-10g/dl), volume status (postural hypotension resolved, but postural dizziness persisted) and exclusion of sepsis (procalcitonin-0.04mg/dl), thyrotoxicosis (free-Thyroxine-T4-1.29ng/dl; TSH-2.8IU/L) and myocarditis (negative transthoracic echo/troponin). Bedside autonomic function testing revealed poor heart rate variability supporting possible cardiac autonomic failure (Figures 5 and 6). Before further investigations could be arranged, she had to be transferred for oncological management. Unfortunately, after the second cycle of chemotherapy, the patient succumbed to neutropenic sepsis.

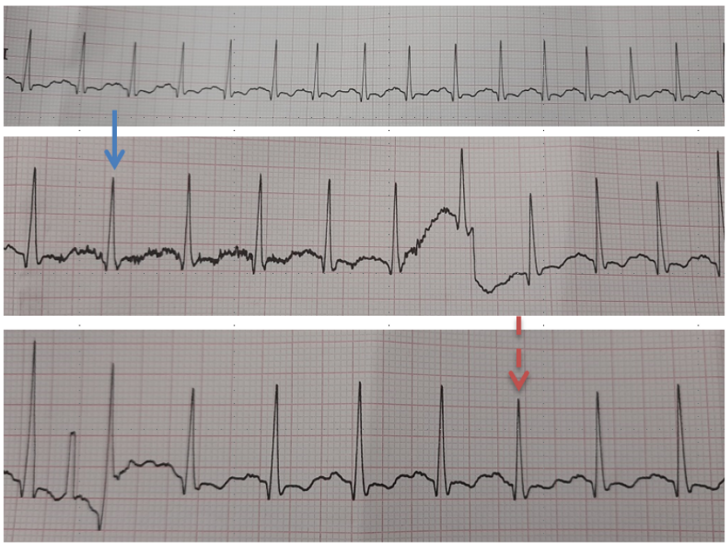

Figure 5. ECG rhythm strip taken during standing.

Line arrow – Beat 15

Dotted arrow – Beat 30

30:15 RR ratio = 0.528s / 0.52s

= 1.015

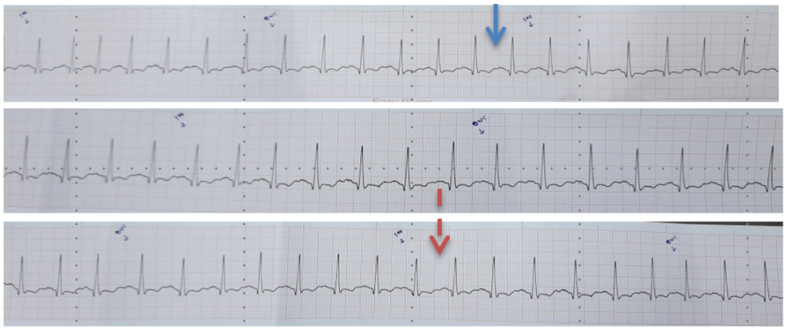

Figure 6. ECG rhythm strip taken during deep breathing.

Line arrow – Longest RR in expiration

Dotted arrow – Shortest RR in inspiration

E:I RR ratio = 0.54s/0.5s

= 1.08

Discussion

This patient presented to us with an aggressive lymphoma resulting in her poor outcome. However, the authors highlight two possible instances where a high index of suspicion might have made a difference. First, during the episode of buttock pain nine months after the transplant, a diagnosis of sacroiliitis was made based on MRI and biochemical evidence. Sacroiliitis can be inflammatory or infectious in nature and as the patient was on immunosuppressants an infectious aetiology was thought of at presentation and she had responded to treatment. However, the resolution was based on reduction in inflammatory markers only and a joint aspiration or repeat imaging were not done. Arthritis including sacroiliitis can be a manifestation of underlying neoplasms, due to direct skeletal deposits or due to paraneoplastic arthritis [3, 4]. Here, the original MR image did not reveal any bony deposit, however the last contrast enhanced CT showed left pelvic skeletal deposits. Five cases reported in the literature highlight that this paraneoplastic sacroiliitis might seemingly respond to targeted anti-inflammatory treatment and there could be a lag of up to 12 months in diagnosing the lymphoma. Above cases have used immunomodulatory treatment, whereas our patient's symptoms responded to antibiotic therapy alone with no escalation of immunosuppression. Bereau *et al*, had encountered sacroiliitis on MRI but a guided biopsy helped diagnose the lymphoma [5].

We postulate the possibility of her original renal disease being a paraneoplastic manifestation. Glomerular diseases are associated with haematological malignancies due to alteration in autoimmune response, T-cell regulatory function and production of cryoglobulins and paraproteins by the latter [6]. A thorough evaluation at the onset might have changed the natural history of both conditions. Immunofluorescence or EM of the biopsy could have given clues regarding the paraneoplastic glomerulonephritis. Despite adequate awareness, unavailability of facilities is a limitation in low resource settings. Treatment of lymphoma might provide sustained remission of the glomerulonephritis [7]. The long lag period between the onset of glomerulonephritis and overt manifestation of lymphoma could have been due to the aggressive immunomodulatory treatment for the primary glomerulonephritis followed by the transplant masking the lymphoma. But the glomerulonephritis could precede the lymphoma by up to five years [8].

Possible autonomic failure manifesting as persistent tachycardia after exclusion of other contributory factors was another point of note. Although it was a terminal manifestation in this case, autonomic failure can precede lymphoma [9,10]. While the treatment of lymphoma might cure the autonomic dysfunction [10], certain chemotherapeutic agents like vincristine might make it worse [11]. Benefit through plasmapheresis via removal of yet unidentified antibodies involved in the pathogenesis is also reported [9].

Conclusions

We emphasise the need for local protocols in evaluation and management of seemingly benign and common conditions, particularly in high-risk populations like organ transplant recipients. In these patients, clinical evaluation, radiological and routine microbiological investigations can be inadequate or misleading. Additional attempts must be made to reach a conclusive diagnosis with ancillary tests performed as determined by the presentation. This will improve identification rates of hidden sinister pathologies like above and will minimise errors due to false re-assurance based on clinical response alone.

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Competing interests

The authors declare no competing interests.

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