CASE REPORT

Acute promyelocytic leukaemia (APL) in a patient with Crohn's disease and exposure to infliximab: a rare clinical presentation and review of the literature

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SUMMARY

With the introduction of potent immunosuppressive and chemotherapeutic medications for various diseases, there is an increased incidence of therapy-related myeloid neoplasms. They are the result of mutational rearrangement and historically, have a grave prognosis compared with de novo myeloid neoplasms. We did a short review on various types of myeloid leukaemias reported after therapy with antitumour necrosis factor and also report, to the best of our knowledge, one among the very few cases of therapy-related acute promyelocytic leukaemia in a patient on infliximab therapy for refractory Crohn's disease. The patient responded well to the traditional treatment and is in complete remission for more than 5 years.

BACKGROUND

It is a very rare and possibly one of the few case reports of acute promyelocytic leukaemia (APL; acute myeloid leukaemia M3, AML-M3) to be reported in a patient with refractory Crohn's disease on maintenance infliximab therapy.

CASE PRESENTATION

A 42-year-old woman with a long-standing history of Crohn's disease had been followed up in the haematology clinic for anaemia. She was diagnosed with iron deficiency anaemia due to chronic diarrhoea and was treated with intravenous iron therapy intermittently. In addition to iron therapy, she was treated with vitamin B₁₂, folic acid and blood transfusions occasionally. Her previous therapy for Crohn's disease included steroids, sulfasalazine, 6-mercaptopurine and azathioprine. Failure to achieve optimal symptom control prompted treatment with infliximab. She was started on standard intravenous induction regimen of 5 mg/kg at 0, 2 and 6 weeks. She responded well to the treatment and was kept on maintenance infusions of infliximab (5 mg/kg every 8 weeks) for approximately 24 months. With intravenous iron supplement, her anaemia improved. Her white cell count (WCC) and platelets were normal. She remained in stable condition for more than 2 years. However, gradually, over a period of few months, it became noticeable that she developed leucopenia and worsening anaemia. Her complete blood count showed WCC 1700/mm³ and haemoglobin 7.6 g/dL. Her platelet count remained normal. These abnormalities prompted a bone marrow biopsy. Flow cytometry analysis of the bone

marrow aspirate revealed 15% blasts/immature cells positive for CD117, CD13 and CD33 blasts, but negative for CD34 and HLA-DR. The immunophenotypical findings were highly suspicious for APL (AML-M3). Two-colour fluorescence in situ hybridisation (FISH) was performed on interphase nuclei using probes for the PML gene on chromosome 15 and the RARA gene on chromosome 17. Juxtaposed signals were present in 10% of the cells, consistent with APL (AML-M3). The bone marrow aspirate smear showed myeloid cells with irregular nuclear contours, indented and bilobed and granular cytoplasm; some with Auer rods were seen (figures 1 and 2). Bone marrow biopsy showed 80–90% cellu-

Figure 1 The bone marrow biopsy section showing moderate cellularity with aggregates of promyelocytes (×400).

Figure 2 High power image showing promyelocytes identified by their relative uniformity with abundant cytoplasm and oval-to-round nuclei that are often eccentrically located (×1000).

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larity with sheets of immature myeloid cells, morphologically compatible with atypical promyelocytes and represented more than 30% of total cellularity. Myeloid maturation was markedly decreased. Residual erythroid precursors and megakaryocytes were present. Routine cytogenetic analysis revealed normal female karyotype. The patient was subsequently admitted to the hospital and received induction therapy with idarubicin and all-trans-retinoic acid (ATRA) with careful monitoring of the coagulation profile and fibrinogen due to the risk of developing disseminated intravascular coagulation. She tolerated the induction treatment without major complications. Repeat bone marrow aspiration and biopsy after blood count recovery revealed less than 2% blasts. The bone marrow was normocellular with a cellularity of 55–60%. All three cell lines were present with good maturation. Flow cytometry was negative. FISH and PCR studies for t(15,17) PML/RAR- α were negative confirming complete molecular remission. She received consolidation treatment with idarubicin and ATRA for two cycles.

OUTCOME AND FOLLOW-UP

The patient remains in remission for more than 5 years. She still follows-up in the haematology clinic for her chronic anaemia and receives intravenous iron treatment and vitamin B₁₂ injection monthly.

DISCUSSION

Therapy-related myeloid neoplasms (t-MN) is a relatively new phrase that has been coined by the WHO to include a series of malignant haematological diseases previously described as therapy-related AML.¹ Chemotherapeutic agents that have been linked to the development of t-MN include alkylating agents and topoisomerase II inhibitors. Other causes of AML include ionising radiation and benzene exposure. Many of the distinct clinical and cytogenetic subtypes of t-MN are the result of preceding cytotoxic treatment. The latency period between cytotoxic therapy and development of t-MN ranges from a couple of months to many years, depending on the dose, duration and kind of preceding cytotoxic therapy. Alkylating agents such as cyclophosphamide and melphalan have a latency period of 5–7 years and are associated with specific cytogenetic abnormalities such as loss of part or all of chromosomes 5 and/or 7. The karyotypes are often complex.² t-MNs caused by topoisomerase-II inhibitors such as anthracyclines, mitoxantrone and etoposide typically result in translocations involving the MLL gene on chromosome 11, band q23 and less commonly, the AML1 gene on chromosome 21, band q22.² In contrast to alkylating agent-associated t-MN, these leukaemias have a much shorter latency of 1–3 years and are not associated with preceding MDS.

The incidence of AML related to non-cytotoxic agents is very rare. There have been a few reports in the literature that have described the development of AML with the use of tumour necrosis factor (TNF)- α inhibitors. Agents that have been reported include etanercept, adalimumab and infliximab. Infliximab is a chimeric IgG 1 monoclonal antibody consisting of human and murine sequences, which have a high affinity towards TNF- α . With the presentation of an antigen, there is an unrestrained response of helper lymphocytes type 1 (Th1) in Crohn's disease because of defective regulation that stimulates the inflammatory response. Researchers have shown that the role of infliximab is not limited the blocking of TNF activity but also has other vital functions such as, involvement in the modulation of TNF-producing cells by complement fixation, antibody-dependent cytotoxicity and apoptosis of T lymphocytes and monocytes,³ and the down-regulation of other proinflammatory cytokines.

Infliximab has been effectively used in various inflammatory conditions such as Crohn's disease, ankylosing spondylitis, ulcerative colitis, rheumatoid arthritis and psoriatic arthritis. Infliximab is being extensively used in all types of Crohn's disease including refractory luminal, steroid dependent and refractory fistulising Crohn's disease. Multiple adverse events have been reported in postmarketing trials such as malignancy, injection site reactions, infusion reactions, demyelinating diseases, heart failure, induction of autoimmunity and serious infections.⁴ Although the risk of these adverse effects is very low, it is important for clinicians to be aware of these side effects. Brown *et al* reported the incidence of eight cases of lymphoma in patients on infliximab from May 1999 to December 2000. Lymphomas are the most common malignancies reported with the use of infliximab and other anti-TNF- α therapy.⁵ A cohort study of 50 000 patients with inflammatory bowel disease carried out in Sweden suggests an increased risk of haematopoietic cancers especially lymphomas, but no trends towards higher risks for myeloid leukaemia were observed in Crohn's disease.⁶ A meta-analysis carried out by Pedersen *et al*⁷ confirmed this observation that there is marginally increased risk of leukaemias with ulcerative colitis, but no such inclination is established with Crohn's disease.

A search of the English literature was carried out through PubMed and Google Scholar using the words 'Acute Myeloid Leukemia after Anti-TNF inhibitors', 'APL', 'TNF alpha inhibitors', 'leukaemia and inflammatory bowel disease' and 'Myeloid leukemias and autoimmune disorders'. The search was focused on articles, reviews and case reports published between years 1980 and 2013. The detailed review of the literature revealed six reported cases of AML after therapy with TNF- α inhibitors (table 1). There was only one reported case of AML-M5 after 5 months of infliximab therapy in a patient with ankylosing

Table 1 Clinical characteristics of reported cases of acute leukaemia after infliximab therapy

Literature search	Disease	Therapy (duration of treatment)	Type of leukaemia
Alcain <i>et al</i> ¹⁰	Crohn's disease	Infliximab (1.5 months)	ALL
Kemta Lekpa <i>et al</i> ¹¹	Ankylosing spondylitis	Infliximab (78 months)	AML M5
Bakland and Nossent ¹²	Ankylosing spondylitis	Etanercept (4 months)	AML M2
Bachmeyer <i>et al</i> ¹³	Psoriasis	Etanercept (4 months)	AML M2
Nair <i>et al</i> ¹⁴	Psoriasis	Etanercept (9 months)	AML
Saba <i>et al</i> ¹⁵	Rheumatoid arthritis	Adalimumab (6 months)	AML
Hong Ki Min <i>et al</i> ¹⁶	Psoriasis	Adalimumab (3 months)	AML
Yano <i>et al</i> ¹⁷	Crohn's disease	Infliximab (not available)	Acute leukaemia
Our patient	Crohn's disease	Infliximab (24 months)	AML M3 (APL)

AML, acute myeloid leukaemia; APL, acute promyelocytic leukaemia.

spondylitis (table 1). Our patient was diagnosed with APL (AML-M3) after 2 years of infliximab treatment for Crohn's disease.

Prior exposure and time duration raised concern that infliximab could be associated with the development of APL (AML-M3) in this young patient. However, other underlying circumstances might also influence disease development. Our patient could have an increased risk for leukaemia due to the presence of an autoimmune disorder. Anderson *et al*⁸ analysed the association of myeloid malignancies with autoimmune disorders and found that autoimmune disease is associated with a significant increase in the risk of AML with an OR of 1.29 (95% CI 1.2 to 1.39). Other authors have compared the incidence of myeloid leukaemia in patients on immunosuppressive therapy for autoimmune disorders and concluded that it is very difficult to ascertain the link between myeloid leukaemia and immunosuppressive drugs, due to the increased risk of developing leukaemia in the setting of autoimmune disease compared with the general population.⁹ All the patients mentioned in table 1 were initially treated with immunomodulators such as thiopurines, before they were started on biologics, so the causal association between the thiopurines and leukaemias cannot be ruled out and needs to be further established.

CONCLUSION

The patient presented here developed APL (AML M3) after a long exposure to infliximab, raising the concern that infliximab may be involved in leukaemia development. The presence of an autoimmune disease such as Crohn's disease may also potentiate leukaemia. It is difficult to define a single aetiology for therapy-related AML because there are multiple host and environmental factors, which can influence the development of leukaemia. However, caution should be drawn from this case and other published case reports that TNF- α inhibitors can be associated with increased risk of AML and lymphomas. Patients should be evaluated promptly if they develop blood count or other haematological abnormalities when they are treated with TNF- α inhibitors.

Learning points

- Tumour necrosis factor (TNF)- α inhibitors should be cautiously used and must be monitored closely for leukaemic complications, even after stopping the drug.
- Acute promyelocytic leukaemia (acute myeloid leukaemia M3) is a rare adverse event with possible associations with TNF- α inhibitors.
- Prompt evaluation is needed if the patient develops abnormal blood counts on being treated with TNF- α inhibitors.

Contributors QD diagnosed and managed the patient and made critical revisions to the manuscript. FM noticed the possible correlation between acute promyelocytic leukaemia and infliximab and drafted the manuscript and AV contributed significantly in manuscript preparation. HH is involved in taking care of the patient. CMS and MTH contributed by providing the pictures and all authors read and approved the final manuscript.

Competing interests None.

Patient consent Obtained.

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