CASE REPORT

Anaemia with inflammation responding to lenalidomide

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SUMMARY

We present a case of a 73-year-old woman with transfusion-dependent anaemia thought to be secondary to an unidentifiable inflammatory condition. Anaemia evaluation including multiple bone marrow biopsies was unrevealing, with the exception of a non-specific elevation of her erythrocyte sedimentation rate and C-reactive protein. She had no identifiable inflammatory condition and did not meet the criteria for myelodysplastic syndrome. She was empirically treated with lenalidomide and achieved a complete response, suggesting that this immunomodulatory drug could potentially have a role in treating a subgroup of patients with immune-mediated anaemia.

BACKGROUND

We present the first case in the literature documenting resolution of anaemia in a patient with anaemia associated with increased markers of inflammation that does not meet the criteria for myelodysplastic syndrome (MDS) and has no clearly identifiable underlying inflammatory condition.

CASE PRESENTATION

A 73-year-old woman with a past medical history of hypertension and stage 1 breast cancer treated without chemotherapy presented with 2 months of progressive dyspnoea on exertion. Complete blood count revealed normocytic anaemia (haemoglobin 7.5 g/dL) with normal white blood cell and platelet counts. A review of her records revealed a haemoglobin level of 11.2 g/dL measured 5 months prior to her presentation. She required 2 units of packed red blood cells every 3–4 weeks despite receiving erythropoietin replacement therapy.

INVESTIGATIONS

Anaemia evaluation revealed mildly elevated ferritin of 381 ng/mL, transferrin 183 mg/dL, serum iron 58 µg/dL, reticulocyte absolute count $0.01 \times 10^3/\mu\text{L}$ at 0.3% with normal levels of B12, folate and lactate dehydrogenase. Protein electrophoresis and immunofixation disclosed a polyclonal pattern without monoclonal paraprotein. Her serum free light chains were elevated with a normal κ to λ ratio. Her liver enzymes, kidney function and serum electrolytes were in the normal ranges. Most notably, she had a markedly elevated erythrocyte sedimentation rate (ESR) at 120 mm/hour and a C-reactive protein (CRP) of 17.7 mg/L. The peripheral blood smear was unremarkable.

An evaluation of the elevated inflammatory markers included imaging with a CT of the chest,

abdomen and pelvis, and laboratory tests with anti-nuclear antibody, creatine phosphokinase, aldolase and a panel of tumour markers.

Although these peripheral studies suggested an inflammatory anaemia, the additional investigation did not reveal any underlying identifiable inflammatory condition. A bone marrow aspirate and biopsy yielded a hypercellular marrow (80%) with myeloid hyperplasia, a plasma cell population of 5–10% with increased histiocytic iron and absent sideroblastic iron; bone marrow aspirate flow cytometry was also unrevealing. Cytogenetic analysis showed a normal female 46, XX. Fluorescence in situ hybridisation (FISH) analysis was negative for 5q31, 7q31, RUNX1T1/RUNX1, MLL, PML/RARA and CBFB 20q11.2 deletions. A repeat bone marrow biopsy at an outside facility could not rule out MDS, myeloproliferative neoplasm versus possible drug or growth factor effect but could not explain her anaemia. The repeat marrow biopsy was moderately hypercellular (50%). Myeloid forms showed full maturation with a mild increase in myeloblasts. Immunostains for CD34 highlighted rare scattered myeloblasts; focal marrow elements were weakly positive for p53 (<5%). The erythroid forms showed full maturation but were markedly decreased. The number of megakaryocytes was normal and there were a few scattered plasma cells. No significant lymphoid infiltrate was seen. A reticulin stain showed a mild increase in reticulin fibres. The aspirate smear showed 3% myeloblasts, 80% myeloids, 3% erythroids, 0% plasma cells, 11% lymphocytes and 3% monocytes. No overt dysplasia was seen. JAK2 V617F gene and MPL W515 and MPL S505 mutations were not detected.

DIFFERENTIAL DIAGNOSIS

The extensive evaluation including traditional peripheral studies and two bone marrow biopsies failed to reveal an identifiable cause for this patient's transfusion-dependent hypoproliferative anaemia. The bone marrow evaluations did not meet diagnostic criteria for MDS and there was no clear evidence of a myeloproliferative neoplasm. The peripheral studies showed a profound inflammatory process as evidenced by the elevated ESR, CRP, ferritin and free light chains. However, other than the anaemia and elevated inflammatory markers, the patient had no symptoms or laboratory evidence suggestive of an identifiable inflammatory condition.

Anaemia of chronic disease (AOCD) is thought to be an immune-mediated phenomenon driven by

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dysregulation of iron homeostasis, impaired proliferation of erythroid progenitor cells and blunted erythropoietin response.¹ AOCD, synonymously termed anaemia of inflammation, presents with an identifiable underlying disease such as acute or chronic infections, rheumatological and inflammatory disorders, malignancy and congestive heart failure and is also thought to share the same pathogenesis as anaemia of acute illness. An immune cascade is thought to originate from these chronic illnesses and results in the release of various cytokines linked to the development of anaemia, including interleukin (IL)-1, IL-6, tumour necrosis factor- α (TNF- α), interferon β and interferon γ .^{2,3} The anaemia is typically mild to moderate and improves with treatment of the underlying disease; transfusions, iron supplementation and erythropoietin replacement therapy are used when treatment of the underlying illness is not achievable. In our patient we were unable to identify and treat an underlying inflammatory condition, her iron stores were adequate and she did not respond to supportive care with erythropoietin replacement therapy.

An immune-mediated mechanism has also been postulated as a potential culprit behind the development of idiopathic cytopenia of undetermined significance (ICUS). The WHO provisional entity of ICUS was coined to describe patients with an unexplained cytopenia in whom the diagnosis of MDS is suspected but not fulfilled.⁴ As such, ICUS is a diagnosis of exclusion and appears to be a heterogeneous entity without a unifying underlying pathophysiology.

TREATMENT

Eight months after our patient's initial presentation we were unable to identify a treatable underlying cause for her anaemia, although we suspected an immune-mediated inflammatory process. She remained transfusion dependent despite erythropoietin supplementation. Although there are no prior cases in the literature to support using lenalidomide in patients not meeting the diagnostic criteria for MDS, we theorised that there might be a benefit to using lenalidomide, an immunomodulating drug, given our suspicion that the patient's anaemia was secondary to an immune-mediated inflammatory state.

We started lenalidomide at a dose of 5 mg daily for 21 out of a 28-day cycle. Over the next 2 months she became transfusion independent with a haemoglobin level of 11.7 g/dL and her ESR declined to 34 mm/hour. She subsequently developed a

grade III diffuse maculopapular rash that resolved with glucocorticoids and discontinuing lenalidomide. About 4 months after discontinuing lenalidomide her symptomatic anaemia recurred with her haemoglobin declining to 8.6 g/dL. She was restarted on lenalidomide at a lower dose of 2.5 mg with resolution of her transfusion-dependent anaemia (figure 1).

OUTCOME AND FOLLOW-UP

Our patient has continued taking lenalidomide 2.5 mg daily for the past 2 years and her haemoglobin has remained in the normal range. She has experienced no additional complications from her therapy and no new information has emerged to explain her anaemia.

DISCUSSION

Lenalidomide, a derivative of thalidomide, is widely used in the treatment of multiple myeloma and MDS with 5q deletion; its role in the management of other malignancies and inflammatory disorders is under further investigation. Multiple different mechanisms of action of lenalidomide have been postulated including a direct toxic effect on tumour cells, anti-angiogenesis and immunomodulation.⁵ The immunomodulatory mechanism involves downregulation of inflammatory cytokines such as TNF- α and upregulation of anti-inflammatory cytokines such as IL-10. Lenalidomide has been shown to stimulate CD8+ cytotoxic T cells and natural killer cells. In vitro studies have shown that CD34+ progenitor cells underwent a dose-dependent increase in cell division when exposed to lenalidomide.⁶ This has been theorised as the mechanism behind recovery in cell counts after treatment of MDS. A randomised phase III trial of 205 patients with red blood cell transfusion-dependent anaemia and low-risk MDS with del5q31 showed that low-dose lenalidomide was effective at achieving erythrocytosis, with 56.1% and 42.6% of patients taking 5 and 10 mg, respectively, attaining red blood cell transfusion independence at ≥ 26 weeks.⁷ Interim analysis on a similar patient population with non-del5q reported a frequency of transfusion independence with low-dose lenalidomide at 26.9% versus 2.5% for placebo at ≥ 56 days.⁸

AOCD is traditionally treated by controlling the underlying inflammatory state or with supportive measures such as iron infusions or erythropoietin replacement therapy. When the underlying inflammatory state cannot be identified or treated

Figure 1 Change in haemoglobin from the initial presentation (month 0) and the daily dose of lenalidomide (Revlimid) received over time.

and the patient does not respond to supportive measures, the treatment options for AOCD are limited.

ICUS appears to be a heterogeneous entity without a unifying underlying pathophysiology and with a varied natural course. Furthermore, the relevant cellular and molecular mechanisms underlying the progression of ICUS to MDS are not well established.^{9 10} In a series of 120 patients with ICUS not making the diagnosis of MDS, 20–62% of cases were found to have mutations in at least one of the 22 sequenced myeloid malignancy genes.¹¹ The frequency of these mutations was higher in patients with some degree of dysplasia. In a retrospective analysis of patients with ICUS eligible for the human androgen receptor assay, clonal haematopoiesis was detected with a clonal X-chromosome inactivation pattern in 6 out of the 23 patients.¹²

In addition to dysplastic clonal processes, immune and cytokine-mediated triggers have been implicated in the pathogenesis of ICUS. Valent *et al* hypothesised that various inhibitory cytokines and regulators of haematopoietic cell growth such as TNF- α or transforming growth factor β could be produced by activated immune cells in an occult inflammatory or neoplastic disease and lead to ICUS.^{9 13} A retrospective study evaluating 166 patients with ICUS who responded to steroids or intravenous immunoglobulin found that 25.9% of the patients had autoantibodies on haematopoietic cells in the bone marrow by western blot analysis, immunofluorescence, flow cytometry and bone marrow mononuclear cell-Coombs test.¹⁴

Our patient's profound anaemia could not be attributed to any other haematological or non-haematological disorders. The multiple bone marrow evaluations including flow cytometry, cytogenetic and FISH analysis did not reveal any dysplasia or clonal process either. Other than anaemia, the elevated inflammatory markers and the polyclonal gammopathy were the only laboratory abnormalities and argue for an underlying immune-related pathology. We could classify the anaemia as AOCD without a clearly identifiable inflammatory cause or ICUS, recognising the apparent overlap between these two diagnostic entities.

Learning points

- ▶ Anaemia of chronic disease is thought to be an immune-mediated phenomenon driven by dysregulation of iron homeostasis, impaired proliferation of erythroid progenitor cells and blunted erythropoietin response.
- ▶ Idiopathic cytopenia of undetermined significance (ICUS) is a distinct clinical entity of unexplained cytopenia where the diagnosis of myelodysplastic syndrome is unmet.
- ▶ The pathophysiology and natural history of ICUS are poorly understood.
- ▶ Multiple different mechanisms of the action of lenalidomide have been postulated with a potential role in cytopenia without dysplasia.
- ▶ Response to lenalidomide with regard to erythrocytosis might be achieved at low doses.

This is the first case report in the literature of lenalidomide treatment for idiopathic anaemia not fulfilling the criteria for MDS. The patient achieved a remarkable complete response to lenalidomide with resolution of her anaemia at the initial dose, recurrence of her anaemia as the medication was withdrawn and subsequent response to restarting lenalidomide at a lower dose. The observed strong temporal relationship between the patient's anaemia and lenalidomide therapy supports the argument that lenalidomide was responsible for the patient's improvement and further suggests that this immunomodulatory drug could potentially have a role in the treatment of a subgroup of patients with ICUS or AOCD with an underlying immune-mediated process.

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Contributors All authors have substantially contributed either to the design of the work or to the acquisition, analysis or interpretation of data for the work, in addition to drafting and revising the work and final approval of the version to be published. In particular, FH and IT contributed to the planning and drafting of the work with JE and AM contributing to the literature review and writing and revision of the manuscript. FH is the identified contributor responsible for the overall content as a guarantor. All authors are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests None declared.

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