

## Unusual presentations of anaemia in aircrew : Case report

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**A**nemia is extremely common in developing countries and its prevalence and etiology is complex. Anemia, like fever, is a symptom of disease that requires investigation to determine its underlying etiology. This could be consequent to a benign nutritional cause at one end or a neoplastic disorder at the other end of the spectrum. Often, practicing physicians overlook mild anemia but it is important to remember that anemia could be the harbinger of a major underlying disorder and should be evaluated completely. Two unusual cases of anemia in aircrew, both haematological malignancies in the early stages, which were picked up on routine medical evaluation are presented in this paper.

### Case 1

SKJ, a 54 year old, symptom free serving officer with unremarkable clinical examination was noted to have haemoglobin of 11.8 gm% on routine evaluation. Further investigations revealed haematocrit of 33%, MCHC 34%, reticulocyte count 1.9%, WBC 6200/cmm; with neutrophils 38% and lymphocytes 56%. The platelet count was normal. ESR was elevated at 54 mm per hour (Wintrob's method). The peripheral smear showed a normocytic normochromic picture with increased Rouleaux formation and no abnormal cells. Urine examination was unremarkable and urinary Bence Jones proteins were negative. The blood urea was 40 mg% with a serum creatinine of 1 mg%. Liver

function tests and serum proteins were essentially normal. Immunoelectrophoresis studies found a large monoclonal serum IgA band (IgA value of 2.5gm/dl). The skeletal survey and bone scan was normal. Bone marrow aspiration was normal; however, the bone marrow trephine biopsy showed 10% plasma cells. Based on the above findings, a diagnosis of IgA Multiple Myeloma, Stage IA was made. The patient was given six cycles of Vincristine, Adriamycin, Dexamethasone (VAD) chemotherapy to which he responded well and went into clinical remission. He was subsequently subjected to autologous stem cell transplant, which was performed successfully. At the time of this report he continues to be in remission 5 years since the onset of disease. After initial observation for 3 years in remission he was reflighted in a multicrew aircraft.

### Case 2

SK, 44 year old male, civil aircrew developed general debility along with easy fatigability and dyspnea on physical exertion. On examination, he was found to be well nourished

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with medium built. There was mild pallor, no icterus or peripheral lymphadenopathy. He had moderate hepatomegaly and splenomegaly. Rest of the clinical examination was unremarkable. Laboratory investigations revealed haemoglobin of 9.1 gm%. Haematocrit was 27%, MCHC 34%, reticulocyte count 0.8%, WBC 8000/cmm; with neutrophils 45% and lymphocytes 41%; platelet count was normal. The ESR was markedly raised at 142 mm per hour. The peripheral blood smear showed a normocytic normochromic picture with no abnormal cells. Urine examination was normal. Urinary Bence Jones proteins were negative. The blood urea was 48 mg% with a serum creatinine of 1.4 mg%. Liver function tests were within normal limits. Total serum proteins were 10 g/dl (Albumin – 3.3g/dl, Globulin – 6.7 g/dl). Immunoelectrophoresis studies found a large monoclonal serum IgM-kappa band. IgM level was 4.87 g/dL. Beta 2 microglobulin levels were normal and cold agglutinin test was negative. The marrow was hypercellular, with 50 percent of cells consisting of plasmacytoid lymphocytes. The serum viscosity was 5.1 cp. Flow cytometric analysis of the marrow showed a monoclonal population of B lymphocytes expressing pan B-cell markers. A MRI skeletogram was normal. Based on above findings a diagnosis of Waldenström's macroglobulinemia was made. He initially underwent plasmapheresis and is presently on Rituximab. He is planned for an autologous stem cell transplant once in complete remission. Pending above outlined therapy, he has been kept off flying.

### Discussion

The most common plasma cell disorders associated with monoclonal proteins (M proteins) are the benign monoclonal gammopathy of uncertain significance (MGUS), multiple myeloma (MM) and Waldenström's macroglobulinaemia (WM). Each results from the clonal proliferation of fully differentiated B-cells, which produce monoclonal immunoglobulins (M proteins) called

paraproteins.

Anemia though common in patients with MM, (observed in over 60% of cases), is noted variably in patients of MGUS and WM [1]. However, it is commonly noted in symptomatic patients with WM. It is generally normochromic and normocytic as was observed in both the cases. Although many mechanisms contribute to the development of anemia in patients with malignant plasma cell disorders, the main mechanism is related to defective red cell production by the bone marrow and cramping up of the marrow by malignant cells, which displace the normal cells [2]. The depressed red cell production is multifactorial and includes the following factors: (a) impaired availability of storage iron (b) inadequate erythropoietin response to the level of anemia and (c) overproduction of cytokines that are capable of inhibiting erythropoiesis. The severity of anemia is one of the important factors in determining the stage and thereby the prognosis of disease in patients with MM [2, 3]. Apart from anemia, leukopenia or thrombocytopenia may be seen individually in 15% cases.

Multiple myeloma is a relatively rare disorder of the elderly, with an incidence of 3 per lakh population; it has a definite male preponderance, 98% of whom are above the age of 40 years. Waldenström's macroglobulinemia also has a male preponderance and in comparison is extremely rare with an incidence of 5-10% of that of MM. Patients with WM may present with anaemia as in the case reported, however the clinical hallmarks are hyperviscosity, splenomegaly and lymphadenopathy [4]. Renal failure and skeletal lesions are uncommon in WM when compared to MM. In patients with MM, renal involvement is seen in 15% at diagnosis while renal failure develops in 50% during the course of disease. Skeletal involvement is very common in cases of MM, noted in 70 – 85 % of cases manifesting as single or multiple osteolytic lesions or diffuse

osteoporosis. However, in 15% of cases the skeletal survey may be normal, as observed in the case reported [3]. Rouleaux formation on the PBF and elevated ESR may be one of the earliest findings in both MM and WM, as were seen in both of our cases [1,3].

Paraproteinemia in MM not only helps establish the diagnosis (>3.5 g/dl of serum IgG or >2.0 g/dl of serum IgA or >1.0 g/24 hours of lambda/kappa light chains in the urine) but also helps in prognostication (IgG kappa MM having the best prognosis and IgD lambda the worst). In terms of prevalence, IgG MM is the most common type followed by light chain variety and then Ig A with IgM MM being extremely rare [1, 3]. WM is characterized by an Ig M paraproteinemia, which is hallmark of the disease (M protein being >3 g/dl). Bone marrow examination reveals plasma cells with abundant basophilic cytoplasm and eccentric nucleus in patients with MM (20 –95% of the marrow cells), whereas WM closely resembles chronic lymphocytic lymphoma and the bone marrow contains 10 –90% plasmacytoid lymphocytes or small matured lymphocytes. Flow cytometry helps in further characterizing the tumor.

MM is presently incurable, progressive and becomes disseminated in 90% of the cases unless treated. The overall median survival is 36 months and the prognosis depends on tumour mass (stage of disease), response to therapy, renal functions and Immunoglobulin class [5]. The response to VAD chemotherapy followed by high dose chemotherapy and BMT / PBSCT when in remission increases the median survival to 5 –7 years [6, 7].

Course of the disease is usually indolent in patients with WM. Asymptomatic patients can be monitored for evidence of disease progression without immediate need for chemotherapy. Patients with progressive disease are being treated with chlorambucil or fludarabine [8]. Recently

Rituximab, the anti-CD20 monoclonal antibody has been found to be effective in 30% of the previously treated patients[8, 9]. Myeloablative therapy with autologous hematopoietic stem cell support in WM has also shown some promise [10].

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