Spectrum of hematological malignancies in aviators - A Clinical Series

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ABSTRACT

Hematological malignancies (HM) include a broad spectrum of malignancies affecting any component of the hemopoetic system. Like other malignant disorders, HM carry considerable morbidity and mortality and in an aircrew may result in disqualification from flying. The present study describes the profile of HM in aircrew with the view to look at their aeromedical concerns. The available medical documents of all the aviators over a period of ten years (Jan 1997 to Dec 2006) were reviewed and those diagnosed with hematological malignancy included in the study. Clinical examination, investigation, treatment and final disposition regarding flying were analyzed. Nine cases of hematological malignancy were diagnosed among aviators (five civil commercial pilots and four Air Force pilots) during the study period. A wide spectrum of disorder was noted with no particular subtype showing a high incidence. Five of the nine cases subsequently returned to flying duties with waivers. The remaining four cases, a case each of Waldenstrom macroglobulinaemia, non-hodgkins lymphoma, hairy cell leukemia and essential thrombocytosis, are still under treatment and continue being unfit for aviation duties. Hematological malignancies can be picked up early in aviators as they undergo stringent periodic evaluation. Reflighting of aircrew after adequate observation is a definite possibility today in light of potential cure for many of these disorders, leading to optimal utilization of highly skilled manpower.

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Key words: Hematological malignancies, aircrew, waiver

Introduction

Airline flight personnel work in a unique environment with exposure to known or suspected carcinogens and mutagens including ionizing cosmic radiation [1]. Increased exposure to cosmic radiation during flight has been suggested as a potential occupational risk factor. Although there is no consistent pattern of cancer noted in aircrew, reports suggest that pilots are at increased risk of malignant melanoma, non-melanoma skin cancer, and acute myeloid leukemia, and that cabin crew is at increased risk for breast cancer and malignant melanoma [2]. The etiology of the observed increase in incidence of some cancers remains controversial because assessment of possible confounders, especially non-occupational exposure factors has thus far been limited.

Hematological malignancies (HM) include a broad spectrum of malignancies affecting any component of the hemopoetic system. Even though rare in the general population (1-4 per 100,000 per year) [3], HM strike individuals across all age groups, but except for acute leukemia it mostly occurs in the middle and older age groups [3,4]. HM, like other malignant disorder carry considerable morbidity and mortality that would lead to permanent disqualification from aviation duties. Hence it is prudent to diagnose and treat these disorders early.

Although there are a few reports in literature about HM in aviators, these are mostly on acute myeloid leukemia, a high incidence of which has

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been noted in aviators [5]. However not much has been written about the fitness and disposition for aviation duties in aviators suffering from HM. Availability of newer modalities of therapy has made complete remission of HM a real possibility. In the current study we have made an attempt to look at the clinical profile and disposition of hematological malignancies detected among the healthy aircrew during the periodic evaluation done at a medical evaluation center.

Material and Methods

A retrospective analysis of available medical documents of civil and Indian Air Force (IAF) aviators between 01 Jan 1997 and 31 Dec 2006 at the Air Force Central Medical Establishment (AFCME), New Delhi was undertaken to look for cases of hematological malignancies. The population under study consisted of asymptomatic, active pilots undergoing flight medical examinations for both ejection and non ejection seat aircraft.

Medical records of those diagnosed to have HM were screened for history, clinical examination and relevant investigations done to arrive at the diagnosis. A detailed record of the initial symptoms and signs which led the Aeromedical examiner to suspect the malignancy was made. The diagnosis and stage of hematological malignancies in all cases was based on standard criteria. A detailed record of the therapy given for each disorder was obtained. A note was made of the follow up period and the tests done during it to monitor the course of disease, side effects of therapy and final disposition regarding flying or non-flying status.

Re-flighting of the aircrew was based on the guidelines issued by the Indian Air Force and office of Directorate General Civil Aviation of India [6]. Aircrew requiring chemotherapy/radiotherapy were initially observed in a non-flying status for at least 2-3 yrs following completion of all modalities of therapy. They were reviewed once in every six months along with opinion of oncologist/ hematologist. Those in complete remission (CR) and with no evidence of any adverse effects of therapy were considered for a restricted flying status initially. Factors considered prior to awarding flying status were the type of malignancy, its clinical stage, systemic side effects of therapy, overall prognosis and availability of markers for early detection in case of recurrence.

Results

In this study spanning over 10 yrs from 04 Jan 1997 to 31 Dec 2006, a total of nine cases of hematological malignancy were detected amongst aircrew. All the nine were males with a mean age at diagnosis of 44.2 yrs (range 29–59 yrs). None had family history of hematological or other malignant disorders. Of the total nine aircrew, five were civil commercial pilots, four were Air Force pilots (two from fighter stream and two from transport stream).

Spectrum of malignancy

A wide spectrum of disorder was noted with no particular subtype showing a high incidence.The type of malignancy, clinical details, investigations and stage at the time of diagnosis are shown in Table 1. There were two cases of Non-Hodgkins Lymphoma (NHL) and one case each of Acute Lymphoblastic Leukaemia (ALL), Chronic Lymphocyic Leukaemia (CLL), Chronic Myeloid Leukaemia (CML), Essential Thrombocytosis (ET), Hairy Cell Leukemia (HCL), Multiple Myeloma (MM) and Waldenstrom Macroglobulinaemia (WM).

Clinical Evaluation

Six cases were found to be symptom free at the time of initial presentation while one case each

Table 1: Clinical manifestations, investigations and stage of hematological malignancy at the time of diagnosis

Age(yrs)	Type of Aircraft	Total Flying (Hrs)	Symptoms Findings	Clinical	Initial Clue to Diagnosis	Diagnosis
35	IAF (Transport)	3300	NIL	Cervical LAP	Clinical exam	NHL
46	IAF (Fighter)	3445	Pain Abdomen	Lump abdomen	Clinical exam	NHL
56	CPL	10.450	NIL	NIL	Raised TLC	CLL
29	CPL	1500	NIL	Cervical LAP	Clinical exam	ALL
34	CPL	2890	NIL	NIL	PBS	CML
44	CPL	4890	Fatigue DOE	Pallor Hepatomegaly Splenomegaly	Low Hb Raised ESR	WM
54	IAF (Fighter)	4020	NIL	NIL	Low Hb Raised ESR	M M
41	IAF (Transport)	3980	NIL	NIL	Raised Platelet count	ET
59	CPL	12,800	NIL	NIL	Low Hb	HCL

IAF-Indian Air Force, CPL-Commercial pilot license, NHL-Non-Hodgkins Lymphoma, ALL-Acute Lymphoblastic Leukaemia, CLL-Chronic Lymphocyic Leukaemia, CML-Chronic Myeloid Leukaemia, MM-Multiple Myeloma, WM-Waldenstrom Macroglobulinaemia, ET-Essential Thrombocytosis, HCL-Hairy Cell Leukemia, Hb-Hemoglobin, DOE-Dyspnea on Exertion, PBS-Peripheral Blood Smear, ESR-Erythrocyte Sedimentation Rate, LAP-Lymphadenopathy.

of NHL, WM and HCL were symptomatic with non specific symptoms in the form of dyspnea, fatigue and pain abdomen respectively (Table 1). Clinical examination revealed cervical lymphadenopathy in two aircrew (one each with ALL and NHL), while hepato-splenomegaly and lump in right lower quadrant of abdomen was noted in aircrew with WM and NHL respectively. Diagnosis of hematological malignancy was suspected based on clinical evaluation in four cases and routine hematological investigations (ESR, Hb estimation, total/differential leukocyte count and peripheral blood smear) in five cases. Except for one case of NHL, which was diagnosed in Stage-II, all the other cases were diagnosed in Stage-I of the illness.

Treatment

All cases, after extensive evaluation, were prescribed definitive therapy (chemotherapy and/or radiotherapy) based on standard protocols for the respective malignancy. Table 2 summaries the therapeutic protocol for the study population. One case of intestinal NHL required surgery (Rt hemicolectomy with ileotransverse anastomosis). Aircrew with hairy cell leukemia was administered chlorodeoxyadenosine (2-CDA), while aircrew with CML (Philadelphia chromosome positive) responded favorably to Imatinib resulting in complete hematological and cytogenetic remission. Except for routine side effects noted during the course of therapy, none of the aircrew had any long-term side effects. No mortality was recorded during the period of observation attributable either to the primary malignant disorder or its therapy.

Final Disposal

Of the total nine aircrew with HM, six achieved complete remission (CR) after standard chemotherapy/radiotherapy, while two are still under going therapy. One 56 yrs old, civil pilot with CLL (Stage-1A) has not been given any therapy and continues to fly with waiver for the past 4 years under close observation with periodic clinical and

Table 2: Disposal of aviators with hematological malignancy

Diagnosis	Basis of Diagnosis	Stage at Diagnosis	Therapy	Initial Disposal	Period of Unfitness	Present Flying status
NHL Diffuse large B cell	HPE	IA	Chemotherapy Radiotherapy	Unfit	03 years	Waiver. Fit multicrew aircraft
NHL Diffuse B cell	HPE	IIB	Surgery Chemotherapy Radiotherapy	Unfit	Under observation post chemotherapy	Unfit
CLL	BM Lymphoid markers	IA	Nil	Waiver	-	Waiver: Pilot in command with qualified pilot
ALL	LN biopsy BM-75% blasts	-	BMF 90 protocol Radiotherapy	Unfit	03 years	Waiver: Co-pilot status
CML	PBSBM Cytogenetics	Chronic phase (ph+)	Imatinib	Unfit	03 yrs	Waiver Pilot in command with qualified pilot
WM	BM Flow cytometry IEP	IIB	Plasmapheresis Rituximab Planned for Autologous SCT	Unfit	Under treatment	Unfit.
IgA MM	BM IEP	IA	VAD- 06 cycles Allogenic SCT	Unfit	03 yrs	Waiver: Fit multicrew aircraft
ET	BM	Chronic phase	Hydroxyurea	Unfit	Under treatment	Unfit.
HCL	BM Flow cytometry	Chronic phase	2 CDA	Waiver	03 yrs	Waiver: Pilot in command with qualified pilot

NHL-Non-Hodgkins Lymphoma, ALL-Acute Lymphoblastic Leukaemia, CLL-Chronic Lymphocytic Leukaemia, CML-Chronic Myeloid Leukaemia, MM-Multiple Myeloma, WM-Waldenstrom Macroglobulinaemia ET-Essential Thrombocytosis, HCL-Hairy Cell Leukemia, HPE-Histopathological Examination, IEP-Immunoelectrophoresis, BM-Bone Marrow, LN-Lymph Node, ph-Philadelphia, DOE -Dyspnea on Exertion, SCT- Stem Cell Transplant, IAF-Indian Air Force, CPL-Commercial Pilot License

hematological evaluation. Of the six aircrew in CR, four (three civil commercial pilots and one Air Force fighter pilot) were returned to flying duties with waivers, after 3 yrs of observation post CR. One fighter stream pilot (a case of NHL) and one commercial stream pilot (a case of HCL) are presently under observation post CR. Two of the aircrew are still on therapy, hence are unfit for aviation duties at present. This includes one 44 yrs old civil pilot with diagnosis of WM who is on maintenance rituximab (planned for autologous stem cell transplant in case of recurrence). A high incidence of leukemias and lymphoma was noted in the present study, a similar pattern has been recorded by Gundestrup et al who recorded a high incidence of acute myeloid leukemia amongst aviators with more than 5000 hours of flying [5]. The study group was too small to draw any conclusion regarding the incidence and prevalence of any particular HM.

HM can present with varying clinical manifestations (Table 3) depending on the component of the blood affected. Majority of our

Table 3: Aeromedical concerns and waiver guidelines for hematological malignancies

Malignancy	Presenting features	Median survival	Azeromedical concerns	Waiver guidelines
NHL [13]	LAP (60%) Constitutional symptoms (40%)	Overall 5 yrs survival of 50-60%. Aggressive NHL curable in about 30-60% of patients, while Indolent NHL is incurable in late stages.	Poor prognosis in late stage NHL Acute incapacitation rare	Waiver possible 3 years after successful treatment of aggressive NHL. Close follow up for CNS involvement and secondary malignancy post therapy
HD [12]	Constitutional symptoms (40%) LAP (80%)	5 yrs survival of 83% Curable in about 80% of patients	Acute incapacitation rare	Waiver 2 years after completion of treatment of Stage I and IIA in remission.
CLL [7]	LAP (87%) Splenomegaly (54%) Abnormal PBS (30%)	Approx 95 mths but progression may be unpredictable	Anemia Immunocompromise Associated malignancies	Waiver possible in early stage with good functional capacity with normal Hb and platelet count
ALL [5,8]	Lethargy, malaise, infection, anemia or hemorrhage	5 yr survival 46% Survival better in young patient (<30yrs) with low WBC (<30,000/mL), and no adverse cytogenetics, who achieve CR within 4 wks.	DIC Anemia Infections Cerebral hemorrhage	H/O childhood ALL compatible with waiver Adults-3 yrs after treatment while in sustained CR. CNS involvement leads to permanent disqualification
CML [14]	Asymptomatic (50%) Splenomegaly (48%) Abnormal PBS (50%)	Age, Hb, and % blasts in BM determine survival. Overall survival reduces from 60 mths to 6 mths in blast crisis	Anemia Immunocompromise Bleeding	Waiver after 1 yr in CR post Imatinib
WM [10]	Anaemia (38%) Hyperviscosity (31%) Asymptomatic (27%)	Age 65 yrs and Hb <10 g/dl reduce survival from 172 mths to 46 mths	Anemia Hyperviscosity syndrome Bleeding	No waiver guidelines available
MM [9]	Bone pain (66%) Anemia (66%) PBS-Rouleaux formation (60%)	Stage-1*-60 mths Stage 2-40 mths Stage 3-15 mths Overall 5 yr survival 28%	Vertebral involvement susceptibility to injury on ejection. Immunocompromise Bleeding Renal failure	3 years after successful treatment
HCL [11]	Pancytopenia (60-85%) Splenomegaly (95%) Hepatomegaly (45%)	Indolent course with 5-10 median survival	Anemia Immunocompromise Bleeding	Waiver after 1 yr in CR

* Durie-Salmon Stage, NHL-Non-Hodgkins Lymphoma, ALL-Acute Lymphoblastic Leukaemia, CLL-Chronic Lymphocytic Leukaemia, CML-Chronic Myeloid Leukaemia, MM-Multiple Myeloma, WM-Waldenstrom Macroglobulinaemia, HD-Hodglins Disease, HCL-Hairy Cell Leukemia Hb-Hemoglobin, DOE-Dyspnea on Exertion, LAP-Lymphadenopathy, PBS-Peripheral Blood Smear, DIC-Disseminated Intravascular Coagulopathy, CR-Complete Remission.

patients (6 out of 9) were asymptomatic and clinical signs raising the suspicion of underlying malignancy were noted in only four of the nine patients at the time of detection of malignancy. Data from various clinical series show that about 10-25% of patients with malignancy may remain asymptomatic during the initial stages of the disease [1,3]. Higher percentage of asymptomatic patients noted in the present study was probably due to the mandatory periodic clinical checks and investigations done in the aircrew, which led to diagnosis at an early stage of disease. Good response to therapy noted in our patients was also attributable to early stage at which malignant disorder was picked up. Natural history of most of the malignant disorders reveals that the cure rate is directly related to the grade and clinical stage of the disease [4].

The major aeromedical concern in case of

aviators is their fitness to continue flying or returning to flying status following successful treatment of the index disorder. Response to therapy varies with the type of HM. Low grade malignancies like CLL, plasmacytomas, monoclonal gammopathy of uncertain origin (MUGS), HCL and WM have good long-term survival, while it is not so good for leukemias and MM [7-11]. In terms of response to therapy at one end of the spectrum we have the acute leukemia and myeloma with less favorable response and high relapse rate while at the other end we have lymphomas and chronic leukemia's with more favorable response [7, 12,13,14]. However the exception to this rule is low grade NHL which is indolent, progressive and responds less favorably to therapy [13]. In disorders like HCL and CML new line of therapy has had good impact on achieving CR and this may have led to early reflighting of the aircrew as was seen in our series [11,14]. It is mandatory to observe aircrew post therapy for a long duration to rule out recurrence, the possibility of which is highest during the first 2 years post CR. This is done to prevent any sudden incapacitation resulting from neurological impairment (intra-cranial bleeding due to thrombocytopenia or disseminated intravascular coagulation and thrombosis due to hyperviscosity). Sudden incapacitation is more likely to be noted with leukemia's and myelomas than with lymphomas [8, 9]. On the other hand certain other symptoms like bone pains (due to proliferating blast cells particularly with myelomas), dyspnea or dysphagia (due to mass effect to of tumor cells as may be seen with lymphomas) may lead to severe morbidity in case there has been recurrence post remission.

Reflighting in aviators with HM is not only dependent on the natural history of the primary disorder but is also dictated by the ill effects of definitive therapy. Ill effects of therapy are both acute as well as chronic; most of the patients receiving anthracycline-based chemotherapy must undergo periodic cardiac evaluation to rule out drug-induced cardiomyopathy [15]. In our study the average period of observation post therapy was 4 yrs and 83% of all treated cases maintained complete remission. Since all our cases were detected in early stages, the prognosis was better and probability of maintaining remission was higher.

It must be stated that ours was a small observational study and it will be not be right to compare our findings with the published literature which have been conducted in a large cohort of hospital based patients. However what emerges from the above data is that not all the patients present with classical signs and symptoms of underlying disease and a high index of suspicion often leads to the diagnosis. Further it was the stringent periodic medical evaluation that led to diagnosis of the underlying malignancy in its early stage making its cure with new therapeutic regimens a possibility. The study also highlights the fact that aviators with HM in CR can be permitted to fly with suitable waivers on a case to case basis.

Hematological malignancies can be diagnosed early in aviators as they undergo stringent periodic evaluation. Re-flighting of aircrew after adequate observation in sustained clinical remission post therapy is a definite possibility today.

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