

From: Bruce Jarnot <jarnotb@api.org>
Sent: Tuesday, February 10, 2004 7:21 PM (GMT)
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Cc: Jmricewas@aol.com
Subject: Shanghai BHRC... HIV infection also correlated with myelodysplasia and AML?
Attach: HIV & myelodysplasia or AML PubMed Jan 04.doc

For your review and consideration, Jerry Rice has uncovered some interesting literature (see attached email and abstracts) suggesting HIV infection may not only be a risk factor for NHL, but also a risk factor for myelodysplasia and possibly AML...

Best Regards - Bruce.

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-----Original Message-----

From: Jmricewas@aol.com [mailto:Jmricewas@aol.com]
Sent: Friday, January 23, 2004 11:50 AM
To: Bruce Jarnot
Subject: Literature on HIV infection, myelodysplasia and AML

Bruce,

After our discussion yesterday I did a quick literature search on myelodysplasia and AML in association with HIV infection, including HIV infection as a primary cause of bone marrow depression and dysfunction. I attach copies of the relevant abstracts I located, together with a short summary of their contents.

It would appear that myelodysplasia is well documented as a consequence of HIV infection, and sometimes is its presenting clinical sign. Although HIV-associated myelodysplasia differs in some ways from primary myelodysplastic syndrome in non-infected individuals, including (presumably) those exposed to benzene, bone marrow depression and myeloproliferative disease are clearly associated with HIV infection and therefore might confound studies of benzene exposures in individuals who present clinically with bone marrow anomalies.

We probably will want to share this attachment, or some modification of it, with the SRP after annual progress reports have been received from Irons and Wong. I expect that the issue of HIV serology in controls will be addressed in those reports, and therefore it will be appropriate to raise this issue in the context of SRP comments on the progress reports.

With best regards,

Jerry

Myelodysplasia and AML in HIV-infected individuals

Abstracts from PubMed, searched 22 January 2004

SUMMARY: Benzene is a well-known bone marrow toxin, and the Shanghai Health Study (SHS) on the leukemogenic and toxic effects of benzene is based in part on the well-known ability of benzene to cause myelodysplasia, aplastic anemia, and acute myeloid leukemia (AML) in human beings. Human immunodeficiency virus (HIV) infection is less widely appreciated as an independent cause of myelodysplasia, aplastic anemia, and AML, but an evolving literature on this association suggests that it is real. HIV, the cause of AIDS, can cause high-grade B-cell non-Hodgkin lymphoma (NHL) in infected individuals. Because HIV is recognized as an independent risk factor for NHL, HIV status has to be ascertained in participants (subjects AND controls) in the SHS Case Control Study to avoid confounding the investigation of benzene exposures as possible causes of NHL and other lymphoproliferative diseases. The papers whose summaries are attached indicate that the SHS studies that focus on molecular epidemiology and progression of diseases involving the myeloid cell lineage may also be affected by the HIV status of participants in those studies, independently of benzene exposures.

Myelodysplasia progressing to AML was noticed in AIDS patients, and in some patients with T-lymphotropic virus infections in addition to HIV, as early as 1986 and before. Myelodysplasia now is increasingly being documented as a complication and possibly a direct result of HIV infection (Napoli et al., 1986; Godwin, 1999; Sutton et al., 2001; Aboulafia et al., 2002; Modest et al., 2002; Patsouris et al., 2003). “Myelodysplastic syndrome” has been reported as possibly the first clinical manifestation in some cases of HIV infection (Morales et al., 1990). A direct role of HIV infection itself in the etiology of myelodysplasia has been suggested by some investigators in recent years (Pulik et al. 1998; Ryu et al., 2001), although differences between HIV-related myelodysplastic features and other myelodysplastic syndromes have been reported (Katsarou et al., 2001). Treatment with anti-AIDS drugs such as AZT may contribute to HIV-related myelodysplasia (Inoue et al., 1997) and this side effect of AIDS treatment needs to be distinguished from myelodysplasia in HIV-infected individuals who have not received such treatment.

These findings provide increased justification for requiring ascertainment of HIV status in both cases and controls in all the epidemiologic studies supported by the SHS.

Acute myeloid leukemias, multiple myelomas, and chronic leukemias in the setting of HIV infection.

Pulik M, Genet P, Jary L, Lionnet F, Jondeau K.

Service d'Hematologie, Centre Hospitalier d'Argenteuil, France.

B-cell lineage-derived high-grade malignant lymphomas are a well-recognized complication of HIV infection. However, isolated cases of unusual hematologic malignancies such as acute myeloid leukemias (AML), multiple myeloma (MM) or plasmacytomas, and chronic leukemias have been reported. This review focuses on these uncommon malignancies supervening in the setting of HIV infection. Eighteen cases of AML have been reported. Extramedullary localizations are frequently noticed. Nontreated patients have a survival of 2.7 weeks, compared with 9.8 months for patients treated with chemotherapy; being HIV-positive is not a contraindication to the treatment of AML. Based on the observed 72% incidence of AML M4 and M5 in an HIV-infected population versus 19% to 36% expected in a non-HIV-infected population, we postulate that the association of AML and HIV is not coincidental. The monocytotropism of HIV, the chronic cytokine-mediated activation of monocytes/macrophages, and the immunodeficiency may explain this association. Twenty-two cases of MM or plasmacytomas have been described, most of them in young patients. Again, extramedullary plasma cell tumors are recorded in many patients. Physiopathologic studies suggest that MM may develop because of an antigen-driven response to the circulating viral antigens. A role for Epstein-Barr virus (EBV) in the pathogenesis, as previously described in high-grade non-Hodgkin's lymphomas, is suggested by the presence of EBV genomes in plasma cell tumors. Finally, a broad spectrum of chronic leukemias derived from B- or T-cell lymphocyte lineage has been reported. These associations seem coincidental.

PMID: 11362062 [PubMed - indexed for MEDLINE]

Myelodysplasia associated with acquired immunodeficiency syndrome.

Ryu T, Ikeda M, Okazaki Y, Tokuda H, Yoshino N, Honda M, Kimura S, Miura Y.

Department of Internal Medicine, Social Insurance Chuo General Hospital, Tokyo.

Two cases of acquired immunodeficiency syndrome with myelodysplasia are presented. Case 1 was admitted because of *Pneumocystis carinii* pneumonia. Mild anemia, thrombocytopenia and hypersegmented neutrophils were observed. After the administration of trimethoprim-sulfame-thoxazole and antiretroviral therapy, pancytopenia progressed. Bone marrow (BM) showed dysplastic hematopoiesis, suggesting human immunodeficiency virus-myelopathy. Case 2 was hospitalized due to progressive multifocal leukoencephalopathy. BM specimen obtained for thrombocytopenia showed myelodysplasia similar to myelodysplastic syndrome, suggesting that HIV may have an influence on hematopoietic progenitor cells.

Publication Types:

- Case Reports

PMID: 11518128 [PubMed - indexed for MEDLINE]

Acute myeloid leukemia in patients infected with HIV-1.

Aboulafia DM, Meneses M, Ginsberg S, Siegel MS, Howard WW, Dezube BJ.

Division of Hematology/Oncology, Virginia Mason Medical Center, Seattle, Washington 98111, USA.

OBJECTIVES: Myelodysplasia is a frequent consequence of HIV infection, but acute myeloid leukemia (AML) is rare. Clinical presentations and outcomes of patients with HIV and subsequent AML are reviewed. **METHODS:** Five HIV-infected individuals who were subsequently diagnosed with AML were evaluated and treated. A further 42 cases of AML among patients with antecedent HIV infection were identified using MEDLINE, AIDSLINE, and CancerLit searches. **RESULTS:** HIV infection was present for a median of 48 months (71-180) before AML was diagnosed and the median reported CD4 cell count was 210×10^6 cells/l. In five instances, a delay in diagnosis occurred when cytopenias were initially attributed to HIV or zidovudine-based therapy. In 45 patients, diagnosis was according to the French-American-British (FAB) leukemia classification schema and in two the FAB type was not specified. M2 ($n = 15$) and M4 ($n = 14$) subtypes represented 64% (29/45) of reported cases. Patients with a CD4 cell count $< 200 \times 10^6$ cells/l ($n = 11$) had a median survival time of 7 weeks, while patients with a CD4 cell count $\geq 200 \times 10^6$ cells/l ($n = 7$) had a median survival of 7 months ($P = 0.005$). Although long-lasting chemotherapy-induced responses were rare, the majority of treated patients did achieve complete hematologic remissions. Treatment-related morbidity did not appear to be excessive. **CONCLUSION:** In the absence of randomized and prospective clinical studies to guide decision making, this analysis indicates that induction chemotherapy may be a reasonable option for selected HIV-infected patients with AML and adequate immune function.

Publication Types:

- Case Reports
- Review
- Review of Reported Cases

PMID: 11919488 [PubMed - indexed for MEDLINE]

HIV and refractory anemia with excess blasts (RAEB).

Modest GA, Cooley TP, Zacks JF.

Boston Medical Center and Boston University School of Medicine, Boston, Massachusetts, USA. gmodest@partners.org

We report the case of a 36 year old man who was hospitalized with pneumonia and pancytopenia with refractory anemia with excess blasts confirmed by bone marrow biopsy. He was subsequently found to have advanced HIV infection. Both the HIV infection and the myelodysplastic syndrome responded to highly active anti-retroviral therapy (HAART) with sustained normalization of his hematologic abnormalities within 79 days. Copyright 2002 Wiley-Liss, Inc.

Publication Types:

- Case Reports

PMID: 12210814 [PubMed - indexed for MEDLINE]

Increased angiogenesis in the bone marrow of HIV-positive patients with myelodysplasia.

Patsouris E, Korkolopoulou P, Androulaki A, Douzinas E, Kosmopoulou O, Kordossis T.

Academic Department of Pathology, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece.

AIM: Little is known about the significance of angiogenesis in the bone marrow of HIV-positive patients with myelodysplastic features (MDF). However, this process has been associated with the pathogenesis of primary myelodysplastic syndromes (MDS). The aim of the study was to investigate angiogenesis in the bone marrow of HIV-positive patients. **METHODS:** Bone marrow biopsies from 28 HIV-positive patients were immunostained for factor VIII and the microvessel density (MVD) was quantitatively evaluated and compared with that of 32 biopsies from patients with primary MDS and to 18 control bone marrows from patients with no evidence of bone marrow disease. **RESULTS:** Bone marrow MVD in HIV-positive patients was similar to that of MDS. However, both groups revealed significantly higher MVD counts compared to those of control bone marrows (MDF vs controls $P=0.022$, MDS vs controls $P=0.001$). **CONCLUSIONS:** Bone marrow from HIV-positive patients with MDF reveals similar microvessel counts compared to those with primary MDS, although both differ significantly from that of control bone marrow. Elucidation of the mechanisms underlying bone marrow angiogenesis in HIV-positive patients, may provide further insights into the pathobiology of AIDS and might be of value for the development of new therapeutic strategies for this disease.

PMID: 12959769 [PubMed - in process]

Acute myeloid leukaemia in human immunodeficiency virus-infected adults: epidemiology, treatment feasibility and outcome.

Sutton L, Guenel P, Tanguy ML, Rio B, Dhedin N, Casassus P, Lortholary O; French Study Group on Acute Myeloid Leukaemia in HIV-Infected Patients.

Service d'Hematologie, Hopital Pitie-Salpetriere, 47 Boulevard de l'Hopital, 75651 Paris Cedex 13, France. laurent.sutton@psl.ap-hop-paris.fr

The epidemiology and clinical outcome of acute myeloid leukaemia in human immunodeficiency virus (HIV)-infected adults is poorly documented. We retrospectively surveyed all French haematology centres for adult acute myeloid leukaemia (AML) cases diagnosed between January 1990 and July 1996 who were found to be HIV-seropositive before or at the time of AML diagnosis. Medical charts were reviewed to determine the stage of HIV infection, the characteristics of AML and the response of AML to chemotherapy. Sixteen cases of AML (13 men, three women) were reported by 12 haematology units. Based on assumptions on the size, age and sex distribution of the HIV-infected population in France, the estimated risk of AML in 1990 to 1996 among HIV-infected adults was twice that of the general population (standardized incidence ratio = 2.05; 95% confidence interval, 1.17-3.34). Two other cases occurring before 1990 were spontaneously notified to the authors and were included in the clinical analysis. At AML diagnosis, the median CD4+ cell count was $275 \times 106/l$ and nine patients had acquired immune deficiency syndrome (AIDS). Fifteen patients were scheduled for remission-induction therapy of AML. No deaths were related to AML treatment. Complete remission was obtained in 11 out of 15 patients. Three patients were long-term survivors: two remain alive in complete remission at 8 years and 9 years, respectively, and the third died of AIDS at 8 years. A CD4+ cell count above $200 \times 106/l$ at AML diagnosis was predictive of longer survival (log-rank test: $P = 0.004$). Like many other malignancies, the incidence of AML appears to be increased in HIV-infected patients. Our results show a twofold higher incidence, although this needs to be confirmed in a specifically designed prospective epidemiological study. Such patients, especially those with CD4+ cell counts above $200 \times 106/l$ at AML diagnosis, should receive remission-induction therapy, which can confer long-term survival.

Publication Types:

- Multicenter Study

PMID: 11298584 [PubMed - indexed for MEDLINE]

Haemophilia. 2001 Jan; 7(1): 47-52.

[Related Articles,](#) [Links](#)

Myelodysplastic features in patients with long-term HIV infection and haemophilia.

Katsarou O, Terpos E, Patsouris E, Peristeris P, Viniou N, Kapsimali V, Karafoulidou A.

Second Regional Blood Transfusion and Comprehensive Haemophilia Center, University of Athens Medical School, Laiko General Hospital, Athens, Greece.

HIV-related bone marrow changes are consistent with myelodysplastic features (MDF). Their pathogenesis may differ from primary myelodysplastic syndromes (MDS) and is associated with various factors including the virus itself or the antiretroviral therapy. In order to evaluate the differences between HIV-related MDF and MDS, the morphological changes in peripheral blood and bone marrow, cytogenetic analysis and the response to anaemia treatment were studied in 158 HIV+ patients with haemophilia and the results were compared with those of 61 patients with primary MDS (31 with RA, 10 with RARS, 11 with RAEB, three with RAEB-t and six with CMML). The eligibility criteria for patients with MDS were primary MDS, Hb levels < 10 g dL(-1), and no significant organ disease. The peripheral blood and bone marrow examination revealed MDF in 44 HIV-infected haemophilic patients (27.8%). The median time from seroconversion was 12.5 years and the mean time under AZT therapy was 44.1 months. Nineteen of these patients (43.1%) had Hb levels < 10 g dL(-1), while neutropenia and thrombocytopenia were observed in 29.5% and 25%, respectively. Every patient of this study with Hb < 10 g dL(-1) received erythropoietin (Epo). There were statistically significant morphological alterations between HIV-related MDF and MDS: hypocellularity, plasmacytosis and eosinophilia were more pronounced in HIV haemophiliacs with MDF, while dysplasia of erythroblasts, megakaryocytes and granulocytes was more frequent in MDS patients. No HIV haemophilic patient with MDF had more than 5% blasts in the bone marrow nor did any develop RAEB or acute leukaemia during the period of this study. The cytogenetic analysis was normal in HIV-infected patients with haemophilia whereas 42.6% of patients with MDS had an abnormal karyotype. Complete erythroid response was achieved with Epo administration in 84.2% of HIV+ haemophilic patients with anaemia compared to 19.7% of patients with MDS. These data suggest that bone marrow changes in long-term HIV patients have different characteristics from primary MDS and constitute the entity for which the name HIV-myelopathy has been proposed in the literature.

PMID: 11136381 [PubMed - indexed for MEDLINE]

AIDS Patient Care STDS. 1999 May; 13(5): 303-5.

[Related Articles,](#) [Links](#)

HIV/AIDS case histories: diagnostic problems. Myelodysplasia in AIDS.

Godwin JH.

Department of Medicine, New York Presbyterian Hospital-Weill Medical College of Cornell University, New York, USA. jgodwin%profsvcs@nyh.med.cornell.edu

Publication Types:

- Case Reports

PMID: 10356810 [PubMed - indexed for MEDLINE]

Int J STD AIDS. 1990 Jan; 1(1): 55-7.

[Related Articles,](#) [Links](#)

Myelodysplastic syndrome occurring as possible first manifestation of human immunodeficiency virus infection with subsequent progression to aplastic anaemia.

Morales CE, Sriram I, Baumann MA.

Department of Medicine, Wright State University School of Medicine, Dayton, Ohio.

Publication Types:

- Case Reports

PMID: 2099201 [PubMed - indexed for MEDLINE]

Lifetime treatment of mice with azidothymidine (AZT) produces myelodysplasia.

Inoue T, Cronkite EP, Hirabayashi Y, Bullis JE Jr, Mitsui H, Umemura T.

Department of Pathology, Yokohama City University School of Medicine, Japan.

AZT has induced a macrocytic anemia in AIDS patients on long term AZT therapy. It is generally assumed that DNA elongation is stopped by the insertion of AZT into the chain in place of thymidine thus preventing the phosphate hydroxyl linkages and therefore suppresses hemopoietic progenitor cell proliferation in an early stage of differentiation. CBA/Ca male mice started on AZT 0.75 mg/ml H₂O at 84 days of age and kept on it for 687 days when dosage reduced to 0.5 mg/ml H₂O for a group, another group removed from AZT to see recovery, and third group remained on 0.75 mg. At 687 days mice that had been on 0.75 mg had average platelet counts of 2.5×10^6 . Histological examination on 9 of 10 mice with such thrombocytopenia showed changes compatible with myelodysplastic syndrome (MDS). A variety of histological patterns was observed. There were two cases of hypocellular myelodysplasia, two cases of hypersegmented myelodysplastic granulocytosis, two cases of hypercellular marrow with abnormal megakaryocytes with bizarre nuclei, one case of megakaryocytic myelosis associated with a hyperplastic marrow, dysmyelopoiesis and a hypocellular marrow and two cases of myelodysplasia with dyserythropoiesis, hemosiderosis and a hypocellular marrow. Above mentioned AZT incorporation may have induced an ineffective hemopoiesis in the primitive hemopoietic progenitor cells, which is known to be seen commonly in the myelodysplastic syndrome.

PMID: 9209318 [PubMed - indexed for MEDLINE]

Comparison of bone marrow and hematologic findings in patients with human immunodeficiency virus infection and those with myelodysplastic syndromes and infectious diseases.

Kaloutsi V, Kohlmeyer U, Maschek H, Nafe R, Choritz H, Amor A, Georgii A.

Pathologisches Institut, Medizinischen Hochschule, Hannover, Germany.

The histologic, hematologic, and morphometric findings of 40 patients positive for the human immunodeficiency virus (HIV) were compared statistically with those of 40 patients with primary myelodysplastic syndromes (MDS) and those of 32 HIV-negative patients with infectious diseases. The severity of anemia and the abnormalities of erythropoiesis in the group of HIV patients were less pronounced than in the group with MDS; megakaryopoiesis showed similarities only with the group of patients with infectious diseases, and characteristics of dysplasia were not observed. Granulopoiesis in MDS showed an increase of blasts in several cases; this was not found in any biopsy specimen from the HIV group. In addition, a statistically significant increase of monocyte-like cells and giant bands could be observed in the bone marrow of the HIV patients. The peripheral blood findings and bone marrow picture in the series of our HIV patients appeared to be related mainly to the influence of opportunistic infections, although a direct effect of the HIV itself could not be excluded.

PMID: 8116565 [PubMed - indexed for MEDLINE]

Am J Clin Pathol. 1986 Dec; 86(6): 788-91.

[Related Articles,](#) [Links](#)

Myelodysplasia progressing to acute myeloblastic leukemia in an HTLV-III virus-positive homosexual man with AIDS-related complex.

Napoli VM, Stein SF, Spira TJ, Raskin D.

Myelodysplastic changes have recently been described in patients with the acquired immunodeficiency syndrome (AIDS). The authors report a patient with AIDS-related complex and myelodysplasia who rapidly progressed to acute myeloblastic leukemia. Infection with human T-cell lymphotropic virus type III (HTLV-III) was documented by culture and by serology. Chromosome studies showed monosomy of chromosome 7 and structural abnormality of the long arm of chromosome 3. The association of HTLV-III infection with myelodysplasia and acute myeloblastic leukemia may have been coincidental in this reported case, but it is also possible that the leukemia was secondary to the HTLV-III infection. Further investigation appears justified.

Publication Types:

- Case Reports

PMID: 3466525 [PubMed - indexed for MEDLINE]