An autopsy study of misdiagnosed Hemato-lymphoid disorders

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Abstract

Hemato-lymphoid disorders can range from simple nutritional anemias to leukemias and lymphomas. Precise analysis of causes of death is needed to focus research efforts and improve morbidity and mortality in Hemato-lymphoid disorders.[1] The morphological evidence of the cause of death was studied in 48 autopsies of hematolymphoid disorders. 16 cases of indolent hematolymphoid disorders were detected which remained undiagnosed during their lifetime and hence were untreated. The clinical presentation and the cause of death in these patients was studied and the reason for such cases being not diagnosed in time was analysed. Most of these patients presented to the tertiary care centre at a very late stage during the course of their disease. Before admission at this tertiary care centre, most of these cases were misdiagnosed as acute febrile illness as the presenting symptom was that of fever.

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Introduction

For more than one century, autopsy studies have offered outstanding benefits to clinical medicine. Macroscopic and microscopic evaluation of organs and tissues at autopsy have not only helped pathologists to understand mechanisms of diseases but also verified clinical diagnoses and provided data for epidemiologists. Hematolymphoid disorders constitute a special group of diseases due to their low incidence, high mortality, complex diagnostic steps that are required for their care and also for the need of aggressive therapeutic methods [2].

Aim

This study aimed to review the autopsy findings seen in hematolymphoid disorders, with an emphasis on the clinical presentation and the cause of death of cases which were misdiagnosed antemortem.

Methods and Materials

Autopsy cases diagnosed as hemato-lymphoid disorders (other than nutritional anemia) Clinically or at an autopsy were included in the study. Detailed case histories were retrieved by going through indoor case papers and noting the ancilliary investigations performed. Morphological features of external & cut surfaces of the organs were documented. After preservation in 10% formalin, adequate sections from each of the organs were taken. Sections were studied by using Haematoxylin and Eosin stain and special stains were used wherever indicated.

In cases which were not diagnosed before the death of the patient, post mortem blood sample was used for the investigations such as complete blood count with peripheral smear, sickling test, solubility test and imprints from the bone marrow, liver, spleen, lymph nodes etc. were studied wherever indicated.

Leukemias were classified and subtyping of lymphomas were done with the help of immunohistochemistry wherever required.

Observations

Out of 48 autopsies of hemato-lymphoid disorders, benign etiology was seen in 25% of the cases and malignant etiology was evident in 75% of the cases. A male predominance (81.25%) was seen. The details of the entities observed are given in Table 1.

Table 1: Distribution of cases encountered in the study

Hemato-lymphoid disorders	Total no. of cases	Cases diagnosed clinically-antemortem	Indolent Cases diagnosed at autopsy-postmortem
Sickle cell anemia(SCA)	07	03(42.8%)	04(57.1%)
Thalassemia major	04	04(100%)	00
Aplastic anemia	01	01(100%)	00
Acute myeloid leukemia(AML)	10	07(70%)	03(30%)
Acute lymphoblastic leukemia(ALL)	06	03(50%)	03(50%)
Chronic myelogenous leukemia(CML)	07	04(57.1%)	03(42.8%)
Chronic lymphocytic leukemia	01	01(100%)	00
Non Hodgkin lymphoma(NHL)	08	05(62.8%)	03(37.5%)
Hodgkin lymphoma	01	01(100%)	00
Myelodysplastic syndrome	01	01(100%)	00
Multiple myeloma	01	01(100%)	00
Langerhan cell histiocytosis	01	01(100%)	00
Total	48	32(66.6%)	16(33.3%)

16 cases (33.3%) out of 48 cases were diagnosed after post mortem examination.
This proportion was significant considering the management options available for treating these conditions.
In our study of 7 cases of sickle cell anemia, 4 cases were diagnosed at autopsy.(Table 2)

Table 2: Observations In cases of Sickle cell anemia

Sr.no, Age(yrs)/sex/ Hospital stay/ Diagnosed	Clinical impression	Post mortem	Mode of death	Significant Post mortem findings
Case1 36/M/ 8hours/	Known case of Sickle Cell Anemia with acute intestinal obstruction	Congestive Cardiac Failure with secondary hemosiderosis of spleen, liver. Cirrhosis-	Congestive Cardiac Failure	Spleen -shrunken, brown, multiple infarcts. Liver-Cirrhosis Kidney-infarct
Case2 26/M/ 1day/AM	Known case of Sickle Cell Anemia with sickle cell crisis	Sickle cell crisis	Sickle cell crisis	Spleen-enlarged, infarct, Liver-enlarged,
Case3 20/M/ 4hours/ AM	Known case of Sickle Cell Anemia with acute intestinal obstruction	Lobar pneumonia, Intestine-unremarkable	Acute chest syndrome	Spleen-enlarged, infarct, Lungs-lobar pneumonia
Case4 25/M/ 10hours/ Diagnosed at autopsy	Severe anemia in a case of Acute Febrile ilIness	Bronchopneumonia with Sickle Cell Anemia	Acute chest syndrome	Spleen-shrunken Lungs-Bronchopneumonia Kidney-Acute Tubular Necrosis
Case5 18/M/ 18hours/ Diagnosed at autopsy	Acute Febrile ilIness with Congestive Cardiac Failure	Lobar pneumonia with Sickle Cell Anemia	Acute chest syndrome	Spleen-shrunken, infarct .Lungs-lobar pneumonia Kidney- Acute Tubular Necrosis
Case6 22/M/ 6hours/ Diagnosed at autopsy	Acute Febrile ilIness with AGN	Massive pulmonary oedema with Sickle Cell Anemia	Acute chest syndrome	Spleen-shrunken Lungs-oedema Kidney- Acute Tubular Necrosis
Case7 25/F/ 1hour/ Diagnosed at autopsy	Congestive Cardiac Failure in a case of severe anemia in a 6 month pregnancy.	Congestive Cardiac Failure	Congestive Cardiac Failure	Spleen-enlarged, ,Prussian blue+ , Heart-cardiomegaly

Cases diagnosed at autopsy had hospital stay of <24hours. 3 of these cases had acute presentation of febrile illness with anemia and thrombocytopenia, with shrunken infarcted spleen. The reduced spleen size along with infarction suggested repeated vaso-occlusive crisis. One patient was a pregnant female with severe anemia and an enlarged spleen. The commonest cause of death in cases of sickle cell anemia was found to be Acute chest syndrome seen in 57.4% cases, followed by congestive cardiac failure(28.5%)

12 cases of hematolymphoid malignancies were diagnosed at autopsy (Table 3). Out of 10 cases of AML, 3 cases (30%) were diagnosed after the postmortem examination. These 3 cases died within 24hours of hospital stay. Congestive cardiac failure (CCF) following severe anemia was the commonest mode of death in 50% of cases followed by Infections (30%) and bleeding manifestation(20%).

Out of 6 cases of ALL, 3 (50%) cases were diagnosed after the postmortem examination. In these 3 cases hospital stay of the patient was less than 24hours and investigations were done after the post mortem examination. CNS manifestations in the form of intracranial bleed and cerebral oedema resulting in death of the patient was evident in 3(50%) cases followed by sepsis, CCF and respiratory failure.

Out of seven cases, three cases of CML were diagnosed at autopsy. Five patients (71.4%) died during the blast crisis and two patients (28.6%) in the accelerated phase. Multiorgan involvement by leucostasis in blast crisis (57.1%) was the commonest cause of death, followed by CNS manifestations(28.5%) in the form of intracranial bleeding and respiratory infections(14.2%)

Out of 8 cases of NHL, 3 cases were diagnosed after postmortem examination based on gross and histopathology. Further immunohistochemistry was done for typing of lymphomas. Hospital stay of these cases was variable from 1 day to 10 days. These 3 patients were misdiagnosed clinically as acute febrile illness probably because of the clinical presentation and mild thrombocytopenia. Generalised lymphadenopathy was seen in one while peripancreatic and mesenteric lymphadenopathy was seen in second while the third case showed primary splenic involvement. IHC was done in 7cases which showed 4 cases of B-cell lymphomas consistently positive for CD20 and 3 cases of T-cell lymphomas with CD3 positivity. Out of the three cases diagnosed after the postmortem examination two cases were labelled as T-cell lymphomas namely Anaplastic large T-cell lymphoma and Angioimmunoblastic T-cell lymphoma. T-cell lymphomas have poor prognosis and detection rate.

Hematolymphoid malignancies diagnosed at autopsy

Sr. no. Age/sex/ Hospital stay	Clinical features	Duration of symp-toms	Investigations	Clinical impression	Post mortem diagnosis
Case1 62/M/ 5days	Fever, abdominal pain, weight loss, cervical swelling	30	Hb-9gm%, TLC-4200/cumm, PLT-97000/cumm	Acute febrile illness with hepatosplenomegaly	NHL(Angio-immunoblastic T-cell lymphoma)
Case2 57/F/ 10days	Fever with chills, abdominal pain, vomiting	20	Hb-5.6gm%, TLC-9800/cumm, PLT-	Acute febrile illness with severe anemia	NHL (Primary splenic DLBCL)
Case3 46/M/ 1day	Fever, loose motion, vomiting, abdominal pain	16	Hb-12.6gm%, TLC14000/ cumm, PLT-85000/cumm	Acute febrile illness with MODS/sepsis	NHL(Anaplastic large T-cell lymphoma)
Case4 10/M/ 3hours	Fever, Neck swelling, Altered sensorium, Cough, rash over body,	15	*Hb-6.3gm% TLC-8900/cumm Plt-98000/cumm Lymphoblasts-48%*	Tuberculous meningitis with pulmonary tuberculosis	Acute lymphoblastic leukemia
Case5 28/M/ 7hours	Fever with chills, vomiting, dyspnea altered sensorium	3	*Hb-4.9gm% TLC-23000/cumm Plt-58000/cumm Lymphobalsts-33%*	ARDS in a case of acute febrile illness.	Acute lymphoblastic leukemia

Case6 60/M/ 3hours	Fever, jaundice, oral & nasal bleeding, altered sensorium, abdominal pain	14	*Hb-6.8gm%, TLC110000/cumm PLT-59000/cumm, Myeloblasts-78%,*	MODS with DIC in a case of malaria /hepatitis/Abdominal kochs	Acute promyelocytic leukemia with Tuberculous lymphadenitis.
Case7 60/M/ 6hours	Fever, abdominal pain, hematemesis, melaena	7	*Hb-4.8gm%, TLC53000/cumm, PLT-98000/cumm Myeloblasts-56%*	CCF/Hepatitis	Acute myeloid leukemia
Case8 6/F/ 2hours	Abdominal pain, dyspnea	5	*Hb-7.3gm% TLC-3000/cumm Plt-39000/cumm Lymphoblasts80*	CCF following severe anemia	Acute lymphoblastic leukemia
Case9 53/M/ 1day	Fever, generalised weakness, vomiting , altered sensorium,	14	Hb-1.9gm% TLC-3100/cumm, PLT26000/cumm.	Sepsis/metabolic encephalopathy with pancytopenia	Acute myeloid leukemia
Case10 65/M/ 2hours	Fever, abdominal distension,	4	*CBC-Hb8.6gm%, TLC115000/cumm,PLT49000/cum*	Acute intestinal obstruction with pneumonia	Chronic myelogenous leukemia
Case11 50/F/ 4hours	Fever, vomiting, weight loss, cough	20	*CBC-Hb-6.6gm%, TLC-87000/cumm*	CCF following severe anemia	Chronic myelogenous leukemia
Case12 60/M/ 8hours	Fever, hematemesis, altered sensorium	5	*CBC-Hb-7.6gm%, TLC87000/cumm PLT90000/cumm*	Alcoholic cirrhosis with left hemiparesis with Subarachnoid hemorrhage	Chronic myelogenous leukemia

Most of these patients (10) died within 24 hours of hospital stay. This restricted in getting the extensive diagnostic work up of the patient including the routine investigations like complete blood count, FNAC and bone marrow biopsy. These patients had history of fever which was present more than 1-2 weeks. Out of these 12 misdiagnosed cases, clinical impression of acute febrile illness was given in 5 cases(41.6%) followed by CCF(25%) and tuberculosis(16.6%) (Table 4). In our study 7 patients out of these 12 missed diagnosed hematolymphoid malignancies had history of fever for >2 weeks duration. They were treated for acute febrile illness before being referred to this tertiary care hospital.

Table 4: Clinical impressions in cases diagnosed after the post mortem examination

Clinical impression	Cases (n=12)	Percentage	Autopsy findings
Tuberculosis	02	16.6%	1. Acute lymphoblastic leukemia 2. APML with tuberculous lymphadenitis
AFI	05	41.6%	1. Angioimmunoblastic T-cell lymphoma 2. Primary splenic diffuse large B-cell lymphoma. 3. Anaplastic large T-cell lymphoma. 4. Acute lymphoblastic lymphoma 5. Acute myeloid lymphoma
Sepsis	2	16.6%	1. Acute myeloid Leukemia 2. Chronic Myelogenous Leukemia
Congestive Cardiac Failure	2	16.6%	1. Acute lymphoblastic leukemia 2. Chronic Myelogenous Leukemia
Alcoholic Cirrhosis	1	8.3%	1. Chronic Myelogenous Leukemia

Many systemic disorders begin with a prodrome characterized by fever and observation ultimately leads to identification of the illness.

Discussion

Most of hemato-lymphoid malignancies present diagnostic difficulties but are typically diagnosed prior to death/autopsy. Malignancies that sometimes are difficult to diagnose, such as chronic leukaemias,

lymphomas, renal cell carcinomas, and metastatic cancers, often are found in patients with fever of undetermined origin (FUO). Fever is a common presenting problem in primary care practice. Often its cause is determined by the presence of associated localized symptoms and its course is self-limited. The role of autopsy in these cases is to identify the immediate cause of death and common complications.

Less frequently, fever occurs without localization of symptoms and is persistent. The concern with these patients is the possibility of occult disease where diagnostic evaluation is warranted. Febrile illnesses of less than 2 weeks' duration are often infectious in aetiology, most frequently viral, or secondary to drug toxicity and a specific diagnosis is sometimes not established. Many systemic disorders begin with a prodrome characterized by fever and medical observation ultimately leads to identification of the illness.

In 1961, Petersdorf and Beeson defined fever of undetermined origin (FUO) as a febrile illness of more than 3 weeks' duration in which temperatures exceed 38.3° C (101°F) on several determinations and no diagnosis is reached after 1 week of intensive evaluation. The purpose of these restrictive criteria is to eliminate most self-limited conditions. Acute febrile illness are often infectious(30%) in aetiology most frequently viral or malarial, neoplastic causes also contribute in 30%. Lymphoma and leukaemia i.e. haemolymphatic malignancies are most frequent neoplastic causes of fever[3]. The patients of NHL are known to present with non-specific symptoms, such as weight loss and fatigue, followed by acute abdomen pain[4]. NHL was clinically not suspected in 3 cases because of the presentation similar to acute febrile illness. The main problem in management of NHL is detecting these tumor as soon as possible with the help of USG/CT because prognosis is related to tumor stage. If we could detect tumors earlier, prognoses would be better. Even if tumors are difficult to remove surgically, chemotherapy should be effective. These patients have weakened immunity and hence are prone to sepsis which can be a major cause of mortality.

Our study was comparable to the study by Shah et al[1] in which most of the misdiagnosed cases had a short hospital stay. This restricted in getting the extensive diagnostic work up of the patient including the routine investigations like complete blood count, FNAC and bone marrow biopsy.

Conclusion

This study proves the outstanding benefits offered by autopsy studies to clinical medicine. This study concludes that Hemato-lymphoid malignancies can present as fever of long duration. If fever is persistent and occurs without localization of symptoms, a differential of hemato-lymphoid malignancies should be considered and managed accordingly.

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