

HISTOPATHOLOGICAL ANALYSIS OF BONE MARROW TREPHINE BIOPSIES IN CASES OF FEVER OF UNKNOWN ORIGIN

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ABSTRACT

Background: Any fever with undetermined etiology and not showing spontaneous resolution in the anticipated period of self-limited infections is known as fever of unknown origin. Bone marrow biopsy is a useful technique for the diagnosis of prolonged fever in immunocompetent patients. The objective of present study was to evaluate bone marrow biopsy findings in fever of unknown origin.

Material & Methods: This was descriptive study carried out in Department of Histopathology & Hematology, Army Medical College, Rawalpindi, National University of Sciences and Technology, Islamabad, Pakistan. Duration of study was one year from January 2014 to December 2014. Bone marrow trephine biopsy was performed on 40 patients.

Results: Out of 40 patients 30 were males and 10 females. The age range of patients was from 7 to 85 years. Age group 20-30 years showed maximum number of patients. The most frequent finding on histopathological analysis was reactive changes (27.5%) followed by chronic granulomatous inflammation (22.5%), atypical mononuclear infiltrate (10%), aplastic anemia, hypocellular marrow and visceral leishmaniasis (7.5% each).

Conclusion: Morphological and histological examination of bone marrow has definitive role in the diagnosis of pyrexia of unknown origin. Nonetheless, yield of diagnosis can be improved if it is combined with other diagnostic modalities including radiological, microbiological and serological investigations.

KEY WORDS: Bone marrow biopsy; Granulomatous inflammation; Visceral leishmaniasis.

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INTRODUCTION

Fever of Unknown Origin (FUO) is the fever not showing spontaneous resolution in the time period anticipated for self-limited infection and the etiology of which cannot be determined in spite of substantial diagnostic efforts.¹ Quite a few of these conditions affect bone marrow directly or indirectly. Bone marrow examination plays an important role in establishing the diagnosis in such cases.²

Over 200 distinct disease entities have been reported to produce long duration fever or recurrent febrile episodes, which have caused difficulties in making diagnosis.¹ Despite the large number almost

all can be classified into five categories namely infectious, neoplasms, collagen vascular disease, miscellaneous, and undiagnosed when cause is not identified. The proportion of patients in each category varies depending upon the geographic distribution, age group, the span of febrile illness and presence or absence of any underlying disease.^{3,4}

Bone marrow biopsy is a useful technique for the diagnosis of prolonged fever in immunocompetent patients. Thrombocytopenia and anemia seem to be correlated with the value of this test.⁵ The response of the bone marrow differs, depending upon infective and non-infective causes. Changes in bone marrow histology resulting from infection and systemic disease can be identified by analysis of morphology and studying the etiology pattern. It can exert great impact in the management of patients with fever.⁶ In this study an attempt has been made to find out the different causes of FUO analyzed on

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bone marrow trephine morphology. The present study was conducted to evaluate the usefulness of bone marrow biopsy findings in diagnosing cause of FUO.

MATERIAL AND METHODS

This was a retrospective descriptive study carried out in the Department of Histopathology and Hematology, Army Medical College, Rawalpindi, National University of Sciences and Technology, Islamabad, Pakistan for one year from January 2014 to December 2014.

A total number of 40 patients were included. The relevant clinical information and details were obtained from the patients, treating clinician and laboratory request form. Patients of all ages and both sexes diagnosed as having fever of unknown origin were included in the study. Patients having nosocomial fever, known HIV infection and with history of hematologic malignancy were excluded. Informed consent was taken. All biopsies were performed at the posterior iliac crest using a Jamshidi needle. Biopsy fragments were kept in formaline for 24 hours and decalcified in 3% nitric acid. This was followed by tissue processing, paraffin embedding and sectioning, staining with haematoxylin and eosin (H&E) and reticulin were done routinely. Special stains like PAS, ZN stain were done when required. Additionally, special stains were also applied when required. All the bone marrow trephine sections were reviewed and evaluated for morphological details. Continuous variables were derived as means and standard deviation while categorical variables were described in percentages and frequencies using Microsoft excel.

RESULTS

A total of 40 cases were evaluated from January 2014 to December 2014. Out of 40 patients 30 were males (75%) and 10 were females (25%). The age of the patients varied from 7 years to 85 years. Age group between 20-30 years showed maximum number of patients. (Table 1) There was male predominance in all the age groups. Most frequent finding on histopathological analysis was marrow showing reactive changes (27.5%) followed by chronic granulomatous inflammation (22.5%) and marrow showing atypical mononuclear infiltrate (10%). Aplastic anemia, hypocellular marrow and visceral Leishmaniasis were present in three cases (7.5%) each. (Table 2)

Figure 1 & 2 showing numerous LD bodies in one case and well formed granuloma in another case.

DISCUSSION

The bone marrow trephine biopsies provide information on specifics of marrow architecture, cellularity, cell distribution and is particularly helpful in diagnosing focal lesions like granulomas, lymphoid or carcinoma infiltrates.⁷ Bone marrow biopsies are important diagnostic tools in reaching an etiological diagnosis in patients having febrile illness particularly in FUO.⁶ In bone marrow biopsy, two type of changes can be detected. Those that are taking place in connective tissue comprising acute and inflammatory processes, as well as immune reactions and those concerning normal hematopoietic cell lines, with possible hyperplastic or aplastic changes in one or more cell lines. The stromal and vascular reactions

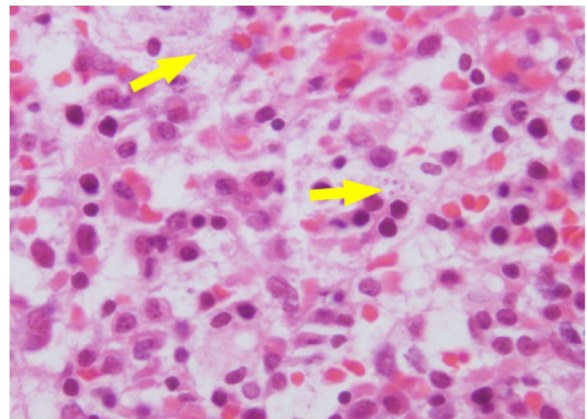


Figure 1: Photomicrograph showing numerous LD bodies in one of the cases. (H&E x400)

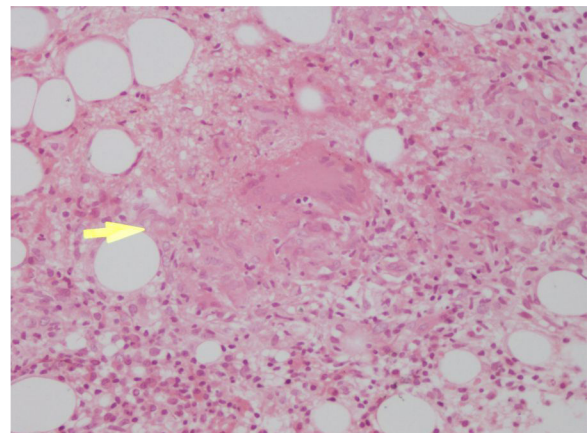


Figure 2: Photomicrograph showing a well-formed granuloma in one of the cases. (H&E x100)

Table 1: Showing age distribution.

No. of cases	<10 years	10-20 years	20-30 years	30-40 years	40-50 years	50-60 years	60-70 years	70-80 years	>80 years	Total
	4	6	15	3	4	3	2	2	1	40

Table 2: Showing percentages of different diseases diagnosed on bone marrow trephine biopsy.

	Male	Female	Total	Percentage	Relative Frequencies
Marrow showing reactive changes	8	3	11	27.5	0.27
Chronic granulomatous inflammation	7	2	9	22.5	0.22
Visceral leishmaniasis	3	—	3	7.5	0.18
Erythroid hyperplasia	—	2	2	5.0	0.05
Hypocellular marrow	2	1	3	7.5	0.18
Aplastic anemia	1	2	3	7.5	0.18
Consistent with infectious process	1	—	1	2.5	0.02
Suggestive of hypersplenism	1	—	1	2.5	0.02
Marrow showing atypical mononuclear infiltrate	4	—	4	10	0.25
Myelodysplastic syndrome	1	—	1	2.5	0.02
Mild myeloid hyperplasia	1	—	1	2.5	0.02
Myelofibrosis	1	—	1	2.5	0.02
Total	30 (75%)	10 (25%)	40		

include myelofibrosis or amyloid deposits.⁸ In, acute inflammation, four main types of variations may be seen namely exudative, hemorrhagic, necrotic and suppurative. Stromal reactions of chronic inflammation and immune reaction in bone marrow include chronic granulomatous inflammation, reactive changes, plasmacytosis, histiocytic hyperplasia, chronic inflammation with fibrosis and amyloidosis.⁸ Many of these inflammatory reaction patterns are non-specific.

According to this study, marrow showing reactive changes is the most frequent finding in patients with FUO as seen in 27.5% of cases (relative frequency 0.275). It is similar to a study conducted by Jha and Sarda which also shows reactive marrow hyperplasia as the most frequent finding in patients with FUO (44 % of cases).⁹

In cases of connective tissue disorders, marrow aspirate shows variable cellularity. Megaloblastic changes can be present and megakaryocytes could be increased or decreased. Some of the patients treated with cytotoxic agents may show features of myelodysplastic changes. Iron stores and myeloid series show variable abnormalities.¹⁰ Myelodysplastic change was diagnosed in one biopsy in the present study as well.

In Visceral leishmaniasis marrow shows several changes which includes presence of LD bodies, decreased myeloid-erythroid ratio indicating relative suppression of myelopoiesis, increased number of plasma cells, presence of giant metamyelocytes indicating suppression of cell division, presence of juvenile megakaryocytes signifying increased

formation of platelets to meet demand caused by increased destruction in hyperactive spleen, presence of micronormoblasts in aggregates indicating splenic hyperactivity and crenated LD bodies with deformed cell membranes in cases of treated kala-azar.¹¹ The cases diagnosed with visceral Leishmaniasis in this study depicted some of the changes like plasma cell prominence and increased number of macrophages. LD bodies were seen in all three cases. None of these cases were clinically suspected to be having visceral Leishmaniasis. In this study it is seen in 7.5% of cases which is similar to a local study conducted by Gandapur and colleagues at Ayub Medical College Abbottabad. According to them, it is seen in 50 out of 570 cases (total 8.7% that constitute 12% of non-malignant causes) with relative frequency of 0.087.¹²

Granulomatous inflammation is a distinct form of chronic inflammation characterized by collection of epithelioid cells, giant cells and surrounded by mononuclear cells with or without caseous necrosis.¹³ Non-caseating granulomas could be present in connective tissue disorders and sarcoidosis. Fibrosis may enclose the granulomas or even penetrate between the cells. Granulomas can be found in lacunar spaces or sometimes in close contact with bone trabeculae. Plasma cells and eosinophil infiltration is often present.⁸ Hemophagocytosis, plasmacytosis, caseous necrosis, and granulomas can be observed in bone marrow of patients with tuberculosis.¹⁴ Chronic granulomatous inflammation is the second most common finding in our study (22.5% of cases). Although, it is contrary to the study conducted by Jha and Sarda that show neoplastic

changes to be the second most common finding.⁹ However, this discrepancy may be due to regional prevalence of specific diseases.

CONCLUSION

Morphological and histological examination of bone marrow has definitive role in the diagnosis of fever of unknown origin. Nonetheless, yield of diagnosis can be improved if it is combined with other diagnostic modalities including radiological, microbiological and serological investigations. When routine investigations fail to reach a specific and conclusive diagnosis, it can readily help in early diagnosis of the disease and its subsequent management.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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AUTHORS' CONTRIBUTION

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Data collection, analysis and interpretation: AZ, AK AS, SQ, SJ
Manuscript writing: AZ, AK AS, SQ, SJ