Journal of Korean Medical Science
Vol. 9, No. 1, 57-63 February 1994

Bone marrow pathology of culture proven typhoid fever

Bo-Moon Shin M.D., In Ki Paik M.D. Han Ik Cho M.D.

Department of Clinical Pathology, Seoul Paik Hospital and Sanggye Paik Hospital, College of Medicine, Inje University and Seoul National University, College of Medicine, Seoul, Korea

The authors analysed bone marrow findings of sixteen cases of culture proven typhoid fever to reveal the pathologic changes according to the disease stage.
The most frequent finding was chronic granulomatous inflammation (eight cases). Infection (bacteria) associated hemophagocytic syndrome (four cases), reactive marrow (two cases), and non specific findings (two cases) were also encountered. Granulocytic hyperplasia with hemophagocytosis appeared at the early stage and was followed by infection (bacteria) associated hemophagocytosis and granuloma in proliferative stage. In lysis (late) stage, granulomatous inflammation was noted. However, resolution of granulomatous inflammation was not distinct. Some nuclear debris and phagocytosis were remarkable in well-formed granulomas.
Thrombocytopenia was the most remarkable peripheral blood finding at the time of biopsy. Anemia, leukopenia, and pancytopenia were also observed in descending order.

Key Words : *Bone marrow, Typhoid fever, Hemophagocytic syndrome, Granuloma, Reactive marrow, Thrombocytopenia*

INTRODUCTION

Typhoid fever is still probably one of the most prevalent infectious diseases in Korea and usually presents itself as a fever of unknown origin (FUO). A bone marrow study is usually done to discover the causes of a FUO. However, bone marrow findings of typhoid fever were usually considered to be nonspecific and were disregarded.

The authors analysed the bone marrow specimens of sixteen cases of culture-proven typhoid fever according to specific disease stages.

Address for correspondence : *Bo-Moon Shin, Department of Clinical Pathology, Seoul Paik Hospital, College of Medicine, Inje University, 85-2-ka, Jur-dong, Chung-ku, Seoul, 100-032, Korea. Tel : (02) 270-0152*
This study was supported by the fund of the Inje Foundation for Research and Scholarship(1993).

MATERIAL AND METHODS

Sixteen bone marrow specimens were taken from fifteen patients. Bone marrow aspiration and biopsy were done at the posterior superior iliac crests and stained with Wright Giemsa and Hematoxylin & Eosin stains, respectively.

Bacterial cultures for *S. typhi* were done with blood, bone marrow, stool, or urine samples. Identification of *S. typhi* was done by API 20E and a serologic test.

RESULTS

1. Clinical findings of the patients

Age distribution was between 20 to 56 years. Male to female ratio was 7 : 8. Fever (15/16), diarrhea including loose stool and hematochezia

(5/16), chill (2/16), and headache (3/16) were the complaints. Hepatosplenomegaly was found in three patients, splenomegaly in two, and hepatomegaly in two. Antibiotics were given to eleven cases before the marrow study.

2. Bacterial culture (Table 1)

S. typhi was isolated from blood cultures in eleven patients, from bone marrow in five , from stool in three and from urine in one. There were five cases which showed positive culture results at more than one specimen (case 7, case 9, case 11, case 14 and case 16). Case 10 and 15 were only positive in bone marrow cultures inspite of negative culture results of their blood specimens.

3. Peripheral blood findings (Table 2)

Thrombocytopenia was observed in eleven cases, leukopenia in six, and anemia (Hb ; below 11.0 g/dL) in seven. Pancytopenia was observed in four cases.

Table. 1. Comparison of specimens of *S. typhi* culture.

Case No	positive specimen	negative specimen
1	stool	urine, blood
2	blood	urine, stool, BM
3	blood	urine, stool
4, 8	blood	urine, stool
5	blood	urine, stool
6	blood	urine
7	blood	urine, stool
9	BM, blood	urine, stool
10	BM	urine, stool, blood
11	stool, urine	blood
12	blood	urine, stool
13	blood	urine, stool
14	BM, blood, stool	urine
15	BM	blood, urine, stool
16	blood, stool	urine

Abbrebiation ; BM : bone marrow

Table 2. Peripheral blood findings of typhoid fever

Case No	Days*	Hb (g/dL)	WBC(/uL)	Platelt(/uL)	poly/lympho
1	8	13.1	2,800	84,000	59/36
2	10	13.7	5,900	122,000	75/15
3	11	13.9	2,400	86,000	56/32
4*	15	8.1	3,400	39,000	86/12
5	16	9.9	3,000	50,000	74/24
6	18	11.9	5,500	77,000	73/23
7	20	10.6	6,600	316,000	42/55
8*	21	10.3	5,900	170,000	73/24
9	25	14.3	4,600	69,000	67/30
10	27	13.8	8,200	126,000	69/17
11	28	9.7	2,700	78,000	59/37
12	30	9.4	2,400	45,000	64/22
13	36	10.2	7,800	90,000	70/26
14	40	11.0	8,500	157,000	67/29
15	42	11.3	6,900	380,000	43/46
16	59	11.1	5,000	344,000	68/30

* Duration from symptom onset to test done

** Case 4 and 8 are from the same patient at 5 days interval

Table 3. Bone marrow pathology of typhoid fever

Case No	Days*	Stage	Bone Marrow Diagnosis
1	8	early	hypocellular marrow with granulocytic hyperplasia
2	10	early	IAHS
3	11	early	normocellular marrow with granulocytic hyperplasia
4*	15	proliferative	IAHS
5	16	proliferative	CGI, ill defined
6	18	proliferative	CGI, well-formed
7	20	proliferative	CGI, ill defined
8*	21	proliferative	IAHS
9	25	proliferative	IAHS
10	27	lysis	hypocellular marrow, no diagnostic abnormalites recognized
11	28	lysis	CGI, ill defined
12	30	lysis	CGI, ill defined
13	36	lysis	CGI, well-formed
14	40	lysis	CGI, well-formed
15	42	lysis	normocellular marrow, no diagnostic abnormalities recognized
16	59	lysis	CGI, well-formed

* Duration from symptom onset to test and the same day of bone marrow biopsy done
** Case 4 and 8 are from the same patient at 5 days interval
Abbrebiation ; IAHS ; infection associated hemophagocytic syndrome CGI ; chronic granulomatous inflammation

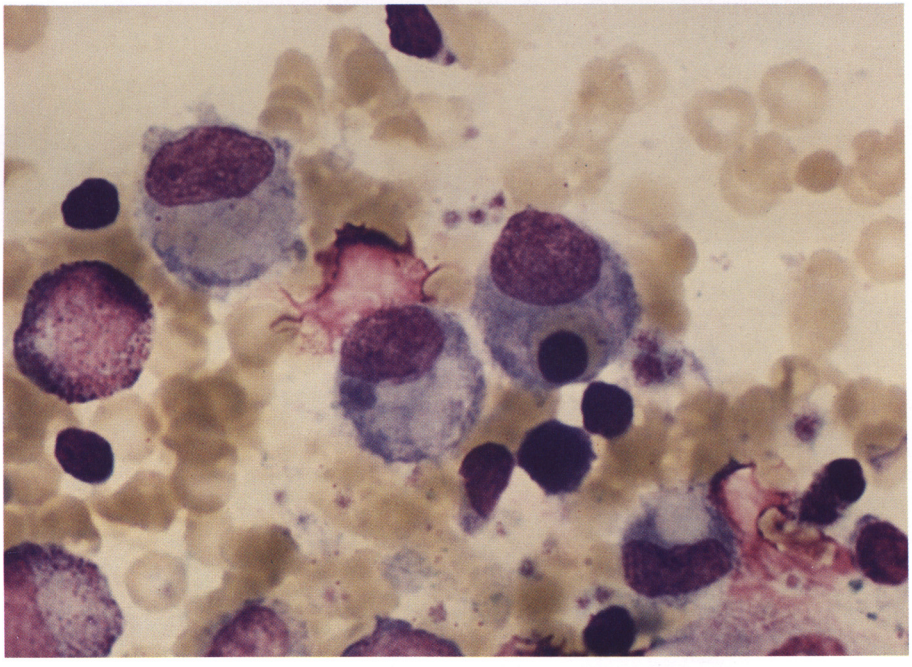

Fig. 1. (Case 9). Bone marrow aspirate showing erythrophagocytic mono-histiocytes. (Wright-Giemsa stain, X 1,000)

4. Pathologic bone marrow findings (Table 3)

The most frequent bone marrow finding was chronic granulomatous inflammation (Fig. 1), which was found in eight cases. Hemophagocytic syndrome (Fig. 2) was found in four cases, and granu-

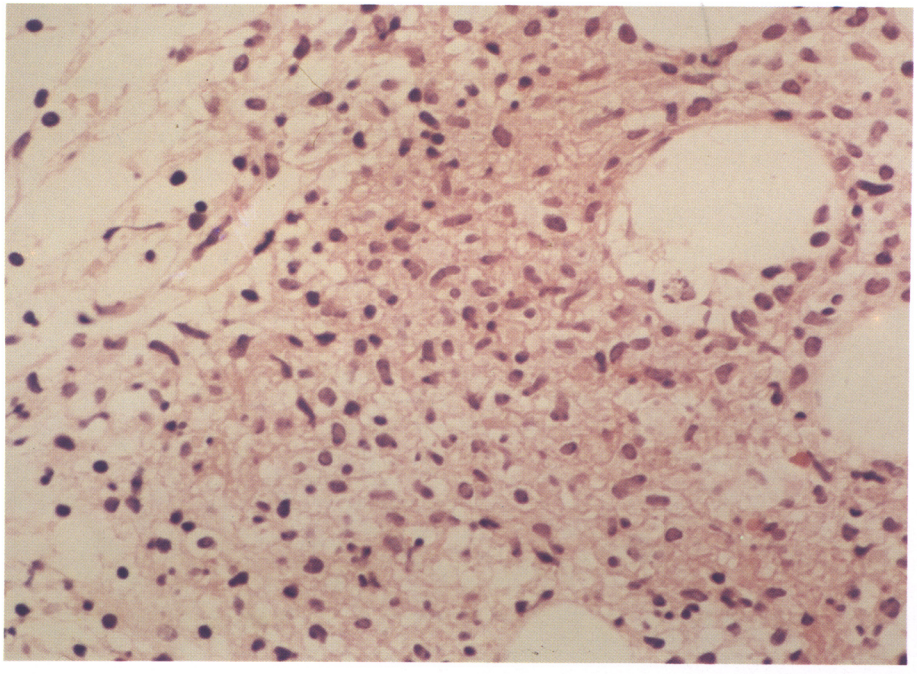

Fig. 2. (Case 6). Bone marrow biopsy showing well-formed epithelioid cell granuloma. (Hematoxylin -eosin stain, × 200)

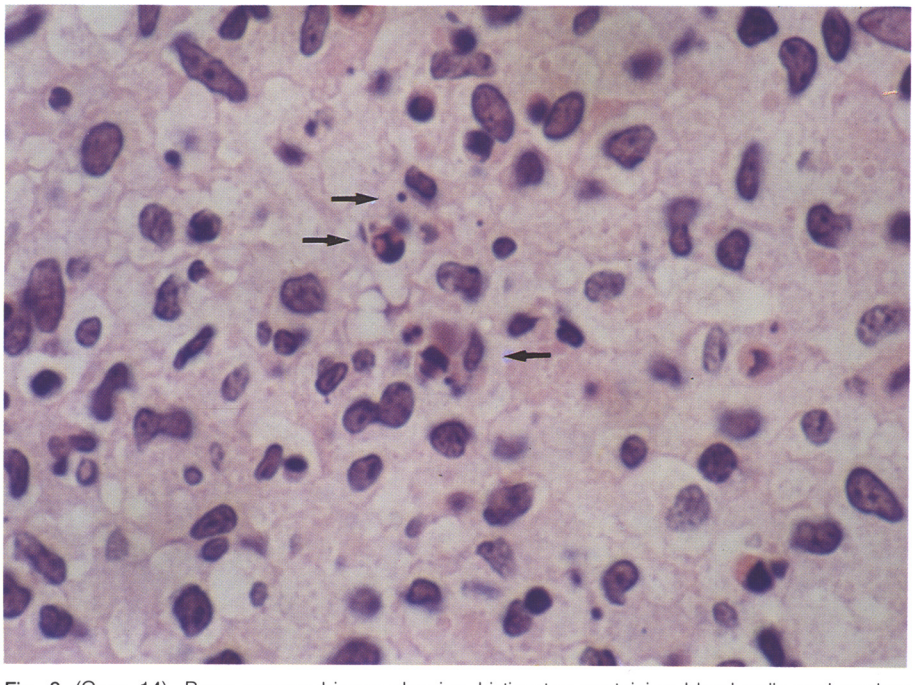

Fig. 3. (Case 14). Bone marrow biopsy showing histiocytes containing blood cells and nuclear debris (arrows) in granuloma. (Hematoxylin-eosin stain, × 400)

locytic hyperplasia in two cases. No significant findings were noted in two cases.

Sequential changes of bone marrow pathology were noted according to the stages of the disease. Authors classified the disease stages according to the days of disease illustrated by Kissane and Anderson (1985) and Hoeprich and Jordan (1989) with some modification.

Based on the symptom onset, early stage is counted till about ten days. The proliferative stage is counted till twenty five days. After then, the lysis (late) stage is followed. Cases 1, 2 and 3 were included in the early stages. Cases 4, 5, 6, 7, 8 and 9 were included in the proliferative stages. The other cases were all included in the lysis stages.

In the early stages, granulocytic hyperplasia was the most significant finding, and mild degree of mono-histiocytic proliferation was accompanied and hemophagocytosis was begun. In the proliferative stage, hemophagocytosis was notable and ganulomatous inflammation was also important findings. In the lysis stage, chronic granulomatous inflammation was typical finding except in one case showing almost normal marrow.

The granulomatous inflammations were divided into well-formed and ill defined granulomas. Well-formed granulomas were found in four cases (cases 6, 13, 14 and 16) and ill defined granulomas were also in four cases (cases 5, 7, 11 and 12). There were no remarkable pathological differences between granulomas in the proliferative stage and in the lysis stage. Well-formed granulomas were mainly composed of epithelioid cells and histiocytes. Phagocytic histiocytes or some nuclear debris were observed in the well-formed granulomas (Fig. 3). Ill defined granulomas were usually composed of histiocytes, plasma cells and lymphocytes.

DISCUSSION

The pathological findings of bone marrow samples of typhoid fever were reported as granulomas (Kissane and Anderson, 1985 ; Lee et al., 1985 ; Robbins, 1984 ; Rywlin, 1976) and infection (bacteria) associated hemophagocytic syndrome (Fernandes and Eintracht, 1979 ; Shin, 1992).

After the incubation period in the gastrointestinal tract, *S. typhi* usually enter the bloodstream and symptoms appear. Then, the pathogen is terminated by reticuloendothelial cells or invades the biliary system (early stage). The proliferative stage, after a week to ten days, is dominated by effects of local bacterial injury, especially in the intestinal tract, mesenteric lymph nodes, spleen and liver, and its duration is usually ten days. After that, the lysis stage (late stage) is followed (Kissane and Anderson, 1985 ; Hoeprich and Jordan, 1989). The authors adopted and slightly modified these disease stages.

In the early stage of the disease, granulocytic hyperplasia with mild histiocytic proliferation was observed. Such bone marrow findings were usually diagnosed as reactive marrows.

In the proliferative stage, active hemophagocytosis was a typical finding and chronic granulomatous inflammation was also observed.

Hemophagocytosis itself is not a specific finding which is frequently observed in malignant histiocytosis (HMR) or virus /bacteria associated hemophagocytic syndromes(VAHS/BAHS). *S. typhi* is a pathogen usually penetrating the reticuloendothelial system including the bone marrow. So, hemophagocytosis is thought to be one of the frequent pathologic findings of typhoid fever in the active proliferative stage. Especially, in areas where the prevalence of typhoid fever is high, hemophagocytic findings should be considered BAHS due to *S. typhi*.

Granulomas were noted in the proliferative or especially in lysis (late) stage, which suggested granuloma probably begin to be formed at proliferative stage and actively formed at lysis stage. Granuloma is one of a special type of chronic inflammations which can be found in bone marrow. Granulomas are classified as either giant cell granuloma, lipid granuloma, epithelioid cell granuloma or mast cell granuloma according to the composed cell types (Frisch, 1985).

Granuloma is not unusual in bone marrow findings. But, there are not many descriptions about the association of typhoid fever and granulomas (Frisch, 1985 ; Kissane and Anderson, 1985 ; Robbins,1984)

In a review of 158 cases of granulomas in bone marrow (Bodem et al., 1983), granulomas were observed in several infectious diseases including tuberculosis, but not typhoid fever. Another detailed paper (Williams and Williams, 1983) about granulomas did not mention typhoid fever as a disease associated with granulomas. However, granulomas

of the bone marrow in typhoid fever were well described in 27 cases of granuloma in Korea(Lee et al., 1985). They revealed granulomas as one type of bone marrow finding in typhoid fever. In their typhoid fever cases, well-formed granuloma was seen in 57% and ill defined granuloma was in 43%, that were similar proportion with our cases.

Although the authors did not study the granuloma in other diseases, there were some remarkable findings comparing with granuloma cases of tuberculosis. Most of granuloma in tuberculosis were well-formed epithelioid granulomas with or without caseation necrosis and Langhans giant cells (Bodem et al., 1983, Lee et al., 1985). These findings showed that well-formed granuloma was relatively high in granulomas of tuberculosis than that of typhoid fever. Caseation necrosis and Langhans giant cells were only found in granuloma of tuberculosis, not in typhoid fever. Nuclear debris and phagocytosis were more frequently found in well-formed granuloma in typhoid fever than in granulomas of tuberculosis.

There were overlapping pathological findings according to the stages of the disease. In cases 1 and 3, which were in the early disease stages, granulocytic hyperplasia was the main pathological finding but a mild degree of histiocytic proliferation (hemophagocytosis) was also observed. Although case 2 was in the early stages, definite hemophagocytosis was observed. Although case 10 was in the proliferative stage, no specific finding except mild hypocellularity was seen. Some degree of histiocytic proliferation or phagocytosis was still observed in case 5, 11, 12, 13, 14 and 16. Such findings suggest that granuloma originated from mono-histiocytic cell proliferation. These overlapping features are probably characteristics of infectious diseases. The immunologic status of patients, the severity of disease , dosage of pathogen and history of drug use were also thought to be important variables (Hoeprich and Jordan, 1989, Williams et al., 1983).

Peripheral blood findings in our studies showed thrombocytopenia as the most remarkable finding (eleven/sixteen cases), regardless of the stage of the disease. Previously leukopenia was described as a usual finding in typhoid fever (Hoeprich and Jordan, 1989 ; Kissane and Anderson, 1985) but in our study, leukopenia was found in only six cases. Anemia was also not a remarkable finding. Pancytopenia was noted in four cases and is probably not an infrequent finding (author's unpublished data).

Furthermore, morphological study of bone marrow with bacterial culture is neccessary for the evaluation of exact pathologic findings of bone marrow in typhoid fever. The means of our study are the basic steps in revealing the pathologic findings of bone marrow in typhoid fever according to the stages of the disease.

CONCLUSIONS

Bone marrow findings of typhoid fever were chronic granulomatous inflammation (eight cases), infection (bacteria) associated hemophagocytic syndrome(four cases), reactive marrow (two cases), and no specific diagnostic abnormalites (one case had rather hypocellular marrow for his age) in two cases.

Sequential changes of bone marrow pathology were noted according to the stages of disease. In the early stages, granulocytic hyperplasia was the most significant finding. Increase of mono-histiocyte and hemophagocytosis or granuloma were observed in the proliferative stages. In the lysis (late) stages, chronic granulomatous inflammation with or without phagocytosis and nuclear debris was noted. However, resolution of granulomatous inflammation was not distinct.

Furthermore, simultaneous morphological and bacteriological studies of bone marrow according to stages of the disease are necessary for the exact interpretation of bone marrow pathology of typhoid fever.

Acknowledgment

The authors would like to express their thanks to Dr. Woo-In Lee for her helpful collection of cases.

REFERENCES

Bodem CR, Hamory BH, Tayer HM, Kleopfer L : *Granulomatous bone marrow disease. A review of the literature and clinicopathologic analysis of 58 cases. Medicine 62 : 372-383, 1983.*

Fernandes CF, Eintracht I : *Histiocytic medullary reticulosis. Lancet 2 : 204-205, 1979.*

Frisch B : *Biopsy Pathology of Bone and Bone Marrow. Chapman and Hall, London. pp. 58-69, 1985.*

Hoeprich PD, Jordan MC : *Infectious disease. J.B. Lippincott Company, Philadelphia. 4th ed. pp. 717-724, 1989.*

Kissane JM, Anderson W.A.D : *Anderson's Pathology. C.V. Mosby Company, St Louis. 8th ed. pp. 303-307, 1985.*

Lee JH, Lee YH, Ahn SH, Choi HS : *Granulomatous bone marrow disease-a review of the hematopathologic analysis of 27 cases-. Kor J Clin Pathol 5 : 515-521, 1985.*

Robbins SL : *Pathologic basis of disease . W. B. Saunders Company. Philadelphia. 3rd ed. pp. 320, 1984.*

Rywlin AM : *Histopathology of the bone marrow. Little, Brown and Company. Boston. 1 st ed. pp. 170-172, 1976.*

Shin BM : *Two cases of bacteria associated hemophagocytic syndrome in typhoid fever. Kor J Clin Pathol 12 : 43-48, 1992.*

Williams G, Williams WJ : *Granulomatous inflammation-a review. J Clin Pathol 36 : 723-733, 1983.*