
OSTEOSARCOMA WITH HIGH SERUM ALKALINE PHOSPHATASE OVER 500 U/L

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ABSTRACT

Twenty two cases of primary osteosarcoma of the bone out of 125 total cases (17.6%) were detected to have over 500 U/L of serum alkaline phosphatase level (AP), which was a very high level as compared to the normal range of 40-105 U/L. There were 13 cases (59.09%) with metastatic disease or terminated by other courses. Only two patients in this group still survive more than 86 and 17 months. Their initial AP were not the highest. The level gradually increased after intraarterial chemotherapy and suddenly turned to normal level after radiation and surgery of the primary bone tumor. In the group of 32 long term survivors among the 125 cases, 13 cases had normal range of AP, only 2 cases had AP over 400 IU. This study, we concluded that if initial serum alkaline phosphatase was over 500 U/L, the disease was more aggressive and tended to metastasize. So different approaches in this group of patients may lead to longer survival.

INTRODUCTION

Elevation of serum alkaline phosphatase in patients with primary osteosarcoma of the bone was observed in less than 50 to 56.4 percent. (1-2) The serum alkaline phosphatase value generally reflects a tendency to new bone formation. The significantly increased level tends to decline to normal level following removal of the primary tumor, or radiation therapy, due to the devitalization of the tumor osteoblast producing the enzyme and a physiological detoxification of circulating enzyme by the liver. (3) The serum AP level always increases when either bone or lung metastasis is detected. There were no previous report mentioned about the information of the patient with the very high serum AP levels. This study reported the nine years experience about the status and the course of disease in 22 osteosarcoma cases who had serum AP level of more than 500 U/L.

MATERIAL AND METHOD

From March 1986 to March 1995, a 125 cases of primary osteosarcoma of the bone were admitted to the Faculty of Medicine, Ramathibodi Hospital. Of these, one hundred and twenty patients had serum alkaline phosphatase levels (AP) recorded. All valued were in International unit with the follow up AP levels except in 16 cases, the values were recorded only once during treatment. All these 16 patients either refused any treatment or lost to follow up after incomplete treatment. Thirty four out of 120 patients (28.3%) had normal or borderline levels of serum AP. The remaining 86 cases had elevated levels, only 22 cases who had the level of serum AP higher than 500 International units, (ranging from 531-5400 U/L) were recruited for this study. Treatment consisted of preoperative intraarterial infusion of cisplatin combined with intravenous chemotherapy, with or without

local irradiation, surgery and prophylactic whole lung irradiation, treatment details were given elsewhere. (4-9)

RESULTS

Among these 22 cases, high initial serum AP was observed in 15 cases. One woman with 143 U/L of AP at the beginning, the level increased to 1140 U/L when she developed lung metastasis 16 months after initial diagnosis. She refused to have her limb amputated and was lost to follow up after 3 courses of intraarterial chemotherapy. She was hospitalized again with lung metastasis with high AP level (case No 5). Other 6 cases had increasing AP level during the course of treatment, all after chemotherapy. Among these patients, all except two, the serum AP level returned to normal after radiotherapy or surgery or combined treatment. Among the two, one had the AP level decreased after another course of chemotherapy (case No 12) while the level of the other is still high after another course of chemotherapy and lost to follow up probably because of dead due to poor general condition and having a very advanced disease (case No 19). Other 4 cases, metastatic disease were detected when the serum AP level increased, 2 metastasized to the lung and 2 to the bone (Table 1 & 2).

For the status of these 22 cases, only 2 patients survived more than 86 and 17 months with a very good health and performance. The first patient, with scapula osteoblastic osteosarcoma, had 90 percent residual tumor after 6 courses of intraarterial cisplatin. He still survives without local recurrence or distance metastasis after 86 months, his serum AP level increased from 2300 IU to 5400 IU after chemotherapy and dropped to 102 U/L after surgery, the level at last follow up was 29 U/L. His erythrocyte sedimentation rate (ESR) dropped from 65 mm/hr. in the past 7 years to 29 mm/hr. in the last visit (case No 1). The other girl with high grade osteosarcoma of distal femur, had her AP level dropped from 1083 IU to 57 IU after radiation and surgery (case No 2). One patients (case No 6) with pelvic chondroblastic osteosarcoma had dramatically decreased in the level of serum alkaline phosphatase after 30 Gy local irradiation (1390 unit to 282 unit)

After treatment, 4 patients had lung metastasis, one also had bone metastasis in addition, the others had local recurrence. In 4 cases, the AP level decreased when intraarterial chemotherapy was started and returned to normal level but increase again when lung

metastasis or local recurrence developed. Another female patient during the course of treatment, her AP level was just 66-143 U/L but rose to 1140 U/L when she had lung metastasis. While the patient developed bony metastasis, the AP level tended to increase as well. In one patient, the AP level was 3965 U/L initially but decreased to a level of 270 U/L after treatment, the level had raised up to 1775 U/L when bony metastasis was detected.

Two patients did not survive even their AP level dramatically dropped from 1056 to 106 and 531 to 63 after treatment respectively.

For the overall results, there were a total of 6 lung and 4 bony metastases. One patient had both lung and bone metastases and the other had lung, bone and cord metastases, while one had local recurrence (Table 2). Eight out of 22 cases had already terminated. One had stable lung lesion after treatment. There were 9 cases which were lost to follow up, 5 with metastatic diseases either only lung lesion or combined with bone metastases, so all of these may be already dead. The other two with high AP level refused treatment after diagnosis.

DISCUSSION

For the total of 120 cases whose serum AP was measured the elevation of serum AP was observed in 86 cases (71.67%). There were only 22 cases with very high level over than 500 U/L. Eight cases (36.36%) in this group had already died. Other 5 cases were suspected to be dead due to metastatic diseases. In the 125 cases of osteosarcoma with AP level studies, 49 cases had lung metastases, 5 bony metastases and 11 multiple metastases with 4 local recurrences.

The reason we set the high level of AP to be over 500 U/L is due to the fact that in normal adolescent during the "growth spurt" with increased osteoblastic activity the serum AP level may also increase by as much as two to threefold that of the normal range, but not over fivefold. (2) Again in condition of bony fracture, serum AP level can also increase to as much as double or triple for a period of several months but not over fivefold. (10)

After surgical removal of markedly bone forming osteosarcoma, the serum AP value returns to normal in a few days. Unless the patient is in a "growth spurt", a renewed rise in AP level is an ominous sign signifying probable recurrence or metastasis. (11) In 1966, McKenna et al described a study of 48 patients in which 79% showed an elevation in the serum AP level 3 months before recurrence or metastasis became

clinically obvious. Serum AP level can be a valuable prognostic indicator of the outcome as well as of effective modes of therapy, such as when switching from one set of chemotherapeutic agents to another (2), although serum AP is not a specific tumor marker for metastatic osteosarcoma and relatively insensitive index of bone turnover owing to the presence of other isoenzyme from hepatobiliary, intestinal and other tissue sources. (10, 12-13) Serum specific bone AP isoenzyme and bone AP are more accurate index of osteoblastic activity but these tests are not yet available in Thailand. However, it might be expected that serum AP higher than 500 U/L which is in a very high level will be correlated with the amount of bony cellular activity especially when the primary tumor is removed, the re-elevation means metastasis. The level of ESR and LDH will be further evaluated to find any possible correlation.

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Table 1 The serum AP level and the status of 22 cases

No	Serum AP Level			Cause of change		Metastasis	Status	survival (mos.)
	initial	maxinum	mininum	increased	decreased			
1	2300	5400	29	after CT	after SX.	No	very well	86 ⁺
2	474	1083	57	after CT	after RT & SX	No	very well	17 ⁺
3	784	804	55	after CT	after SX	lung	stable	6 ⁺
4	531	531	63	-	after CT	unknown	dead	43
5	143	1140	66	lung metastas	-	lung	dead	27
6	1271	1390	94	after CT	after RT	bone	dead	17
7	516	516	-	-	-	bone	dead	17
8	1231	1231	198	-	after CT & SX	lung bone	loss	15
9	3965	3965	270	-	after RT & SX	bone progressed	dead	14
10	700	700	82	-	after CT, RT, SX	bone	dead	14
11	964	964	86	local recur	after SX	local recur	dead	14
12	888	1265	60	after CT	after 2nd CT	unknown	loss	13
13	564	564	40	-	after CT	lung	loss	12
14	597	597	190	-	after CT	lung	loss	12
15	1415	1415	-	-	-	lung, bone spinal cord	dead	6
16	3040	3040	1830	-	after CT	unknown	loss	3
17	773	773	196	-	after CT	lung	loss	3
18	1056	1056	106	-	after CT	unknown	loss	3
19	970	1350	970	after CT	-	unknown	loss	3
20	595	595	-	-	-	lung	loss	1
21	865	865	-	-	-	unknown	No Rx	-
22	555	555	-	-	-	unknown	No Rx	-

CT = chemotherapy, SX = surgery, RT = irradiation

Table 2 End results of 22 cases of high AP level

Survived	2
lung metastases	6
bony metastases	4
lung, bone metastases	1
lung, bone, spinal cord metastases	1
local recurrence	1
unknown condition	7
Total	22 cases

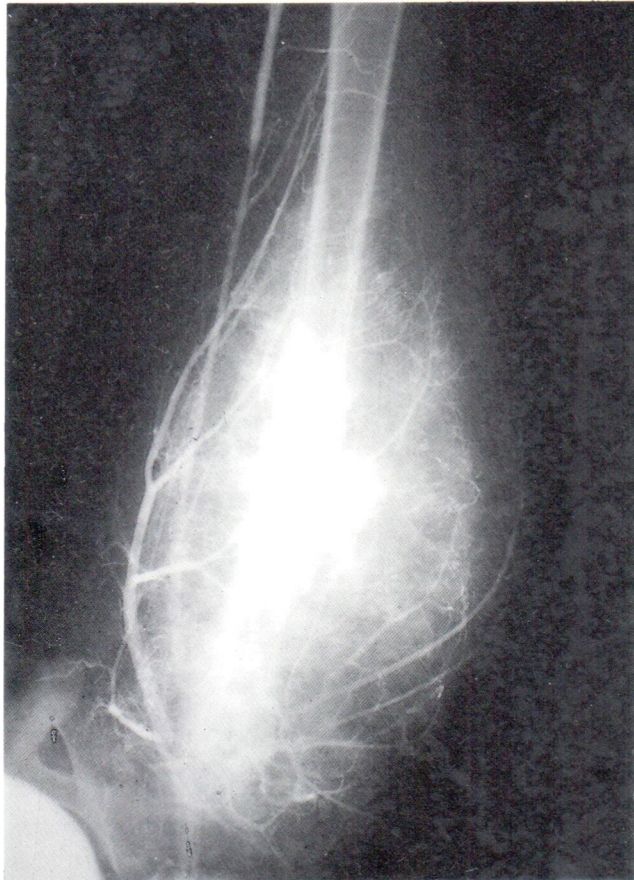


Fig. 1. Angiography of a 10 years boy, with chondroblastic osteosarcoma of his right femur. His initial serum AP was 3040 U/L and decreased to 1830 U/L after 100 mg IA cisplatin and 50 mg epirubicin IV.