

Low serum alkaline phosphatase activity in Kikuchi-Fujimoto disease

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Abstract

Various laboratory findings are helpful in making a diagnosis of Kikuchi-Fujimoto disease (KFD); however, they are not specific. We found decreased serum alkaline phosphatase (SAP) activity in children with KFD. The levels of SAP fell in the acute phase and recovered during convalescence. We conclude that low SAP activity is a characteristic of KFD and may be an auxiliary diagnostic marker for the disease.

Abbreviations: KFD = Kikuchi-Fujimoto disease, SAP = serum alkaline phosphatase.

Keywords: Kikuchi-Fujimoto disease, serum alkaline phosphatase

1. Introduction

Kikuchi-Fujimoto disease (KFD) was first reported in Japan in 1972.^[1] It is a self-limiting and benign disease, characterized by pyrexia and cervical lymphadenopathy with tenderness.^[2] Although the cause of KFD is not yet known, it is possible that infectious triggers influence the etiology of the disease. The finding of KFD is made by histological diagnosis upon excisional biopsy to rule out the differential diagnoses.^[3]

Leukocytopenia, an elevated level of lactate dehydrogenase, and a slight increase in C-reactive protein are helpful in making a diagnosis of KFD,^[4] but these findings are not very specific. Incidentally, we found that serum alkaline phosphatase (SAP), which was used to monitor hepatic damage, decreased in the acute period and rose in the recovery period of KFD. Notably, there have been no reports in the literature focusing on the changes in the levels of SAP in KFD thus far. Therefore, the phenomenon is thought to be a potential characteristic feature of KFD and important in elucidating the pathogenesis of the disease.

2. Materials and methods

2.1. Patients

We examined 14 patients with KFD including 11 boys (1.5–15 years' old) and 3 girls (10–13 years' old). Four cases in which a

positive diagnosis was made based on the pathological findings of cervical lymph node biopsy were called definitive KFD. Their parents gave written informed consent for the biopsy. Ten cases in which a diagnosis was made based on clinical findings integrating cervical lymph node swelling with tenderness, leukocytopenia, negative serology titers for Epstein-Barr virus (enzyme immunoassay [EIA]), cytomegalovirus (EIA), *Bartonella henselae* (indirect fluorescent antibody method [IFA]), herpes simplex virus (EIA), toxoplasma (IFA), and human immunodeficiency virus (EIA), negative for tuberculosis by interferon-gamma release assay, negative for antinuclear antibody, and ultrasonography and/or magnet resonance imaging findings of the cervical lymph node were called clinical KFD. The study protocol was approved by the Institute Review Board of Nihon University Nerima-Hikarigaoka Hospital in which we formerly worked.

The four cases of definitive KFD included 3 boys (1.5–12 years' old) and 1 girl (10 years' old). The ten cases of clinical KFD included 8 boys (6–15 years' old) and 2 girls (11–13 years' old).

2.2. Methods

Alkaline phosphatase activity (IU/L) was measured by the Japan Society of Clinical Chemistry reference method.^[5] Because SAP activity is variable in childhood, we evaluated it in comparison with the normal reference range of Japanese children according to age.^[6] We defined low SAP activity as <430 IU/L of alkaline phosphatase in children of either sex aged 1 to 12 years. Additionally, low SAP activity in girls 14 to 15 years' old was defined as <270 IU/L, and low SAP activity in girls 11 to 13 years' old was defined as 220 to 400 IU/L.

We compared SAP activity levels at the initial visit with the lowest SAP level during illness in 12 KFD patients, including 9 boys (1.5–12 years' old) and 3 girls (10–13 years' old). Two boys (8 and 15 years' old) only had SAP activity measured at the initial visit.

2.3. Statistical analysis

Results are presented as the mean \pm SD or mean \pm SE as indicated in the text. As the results contain a limited number of cases with biopsy-confirmed disease (4 patients), presentation of statistical analysis for this group is not appropriate.

Editor: Steven Callens.

No funding was secured for this study.

The author has no financial relationships relevant to this article to disclose.

The author has no conflicts of interest to disclose.

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Medicine (2017) 96:9(e6228)

Received: 2 September 2016 / Received in final form: 30 January 2017 /

Accepted: 31 January 2017

<http://dx.doi.org/10.1097/MD.0000000000006228>

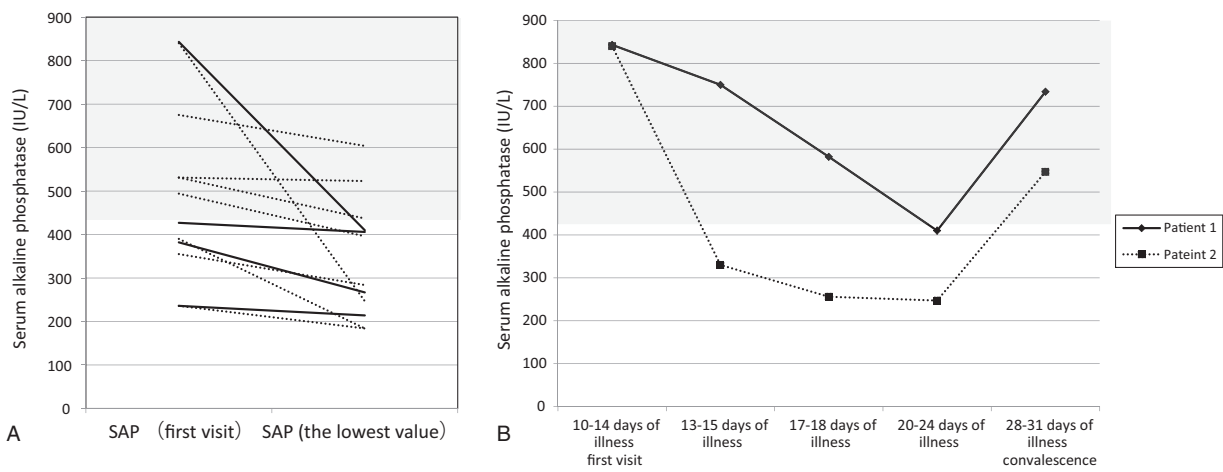


Figure 1. Low serum alkaline phosphatase activity in Kikuchi-Fujimoto disease. (A) Comparison of SAP levels at the initial visit and the lowest levels during illness in 12 KFD patients. The shaded area indicates the normal reference range. The minimum of the normal reference range is 430 IU/L SAP in the age range 1 to 12 years in both sexes. Solid lines represent the SAP activity of definitive (histopathological) KFD patients. Dotted lines represent the SAP activity of clinical KFD patients. (B) The change in levels of SAP activity during illness in 2 representative cases. The shaded area indicates the normal reference range as per Fig. 1A. SAP activity levels of patient 1 (definitive KFD) were determined on days 14, 15, 18, 24, and 31 of illness. SAP activity levels of patient 2 (clinical KFD) were determined on days 10, 13, 17, 20, and 28 of illness. KFD=Kikuchi-Fujimoto disease; SAP=serum alkaline phosphatase.

3. Results

Among the 15 patients examined, 7 patients consisting of 3 definitive KFD cases and 4 clinical KFD cases already had low SAP levels (ranging from 236 to 427 IU/L) at the initial visit. Furthermore, 9 patients, consisting of 4 definitive KFD cases and 5 clinical KFD cases, demonstrated low SAP levels (ranging from 184 to 410 IU/L) after the initial visit. Three patients did not demonstrate low SAP levels or a 10% decrease in SAP levels in comparison with SAP levels at the initial visit.

Overall, in 12 KFD patients, the SAP activity tended to decrease from the initial visit (519.4 ± 206.7 IU/L) during the illness (lowest activity, 374.4 ± 152.8 IU/L) (Fig. 1A). The maximum change in SAP activity of the definitive (histopathological) and clinical KFD groups is shown separately in Table 1. Furthermore, the change in SAP levels over the course of the illness is shown in representative patients with definitive and clinical KFD in Figure 1B, highlighting how the level of SAP decreased in the acute period and increased in convalescence. The

duration of fever and laboratory data of the definitive and clinical KFD patient groups are compared in Table 1.

4. Discussion

An increase in SAP activity is well known in hepatobiliary diseases, bone metabolic diseases (i.e., rickets and hyperparathyroidism), and hyperthyroidism. In contrast, a decrease in SAP is limited to a few diseases (hypophosphatasia, zinc deficiency, vitamin C deficiency, and Wilson disease with hemolytic anemia).^[7] Notably, low SAP activity is not recognized as part of the differential diagnoses for KFD, that is, tuberculosis, systemic lupus erythematosus, cat scratch disease, non-Hodgkin lymphoma, and Kawasaki disease.

Decreased SAP activity is known to be present in low zinc conditions because alkaline phosphatase is a zinc-dependent enzyme.^[8] Low SAP activity in KFD is transient and the level of SAP recovers upon convalescence. Although it is possible that low zinc levels in the acute period of KFD is associated with acute

Table 1
The duration of fever and laboratory data of patient groups with definitively (histopathologically) and clinically diagnosed Kikuchi-Fujimoto disease.

	Definitive KFD (N=4)	Clinical KFD (N=10)
Sex (male/female)	3/1	8/2
Age, y*	9.5 (1.5–12)	11 (6–15)
Duration of fever (days)†	26 ± 3.9 (13.5–38.5)	20.5 ± 3.1 (13.6–27.5)
WBC, cells/μL	2700 ± 570.1 (885.7–4514.3)	2600 ± 215.3 (2120.0–3079.8)
LDH, IU/L	347.3 ± 57.3 (165.0–529.5)	387 ± 38.8 (300.5–473.5)
Ferritin, ng/mL	250.6 ± 70.0 (27.8–473.5)	187.6 ± 23.6 (134.2–241.0)
CRP, mg/DL	0.49 ± 0.20 (–0.14–1.12)	0.81 ± 0.31 (0.13–1.50)
Change in SAP (initial minus lowest level), IU/L	147.8 ± 97.6 (–162.9–458.4)	140.4 ± 59.3 (3.8–277.1)
		‡(N=8 males)

95% CI=95% confidence interval, CRP=C-reactive protein, KFD=Kikuchi-Fujimoto Disease, LDH=lactate dehydrogenase, WBC=white blood cell count.

* Age presented as the median and range, and all other data presented as the mean ± SE (95% CI).

† Fever was defined as body temperature >38°C (axillary temperature).

‡ Eight male patients out of 10 patients with clinical KFD were able to calculate the changes in SAP.

inflammation, we could not confirm low serum levels of zinc in our patients with KFD (data not shown).

Alkaline phosphatase is important in bone formation in childhood. Bone alkaline phosphatase is a more specific maker of osteoblast activity than SAP,^[9,10] but was not examined in our study. We incidentally found low SAP activity in KFD, but the mechanism involved remains unclear. We speculate that the activity of osteoblasts might be temporarily suppressed by a pathological mechanism in KFD. Low SAP activity could therefore be closely related to the pathogenesis of KFD. The responsible mechanism is expected to be clarified in future studies.

Moreover, low SAP activity could be useful to assist in the diagnosis of KFD because it is present in only a few specific diseases. Therefore, low SAP activity, when detected in the context of prolonged fever, leukocytopenia, and cervical lymph node adenopathy with tenderness, may be a strong cue for a diagnosis of KFD.

5. Limitations

The population is too small to draw a general conclusion from. Furthermore, the population was mostly diagnosed with KFD based on clinical findings. Because many diseases should be considered in the differential diagnosis of KFD, clinical KFD diagnosed without excisional biopsy is not as exactly pathologically diagnosed as definite cases. Therefore, the findings from this study should be followed up with a larger study containing more definitive KFD cases.

6. Conclusions

We conclude that low SAP activity is a characteristic of acute KFD and may be an auxiliary diagnostic marker for the disease.

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