Prostatic acid phosphatase (PAP): a possible diagnostic marker of intravascular large B-cell lymphoma

Background and objective: Intravascular large B-cell lymphoma (IVL) has been treated as fever of unknown origin (FUO), and many patients have been treated inadequately based on incorrect diagnoses. We previously experienced a patient with IVL who tested positive for prostatic acid phosphatase (PAP), a marker of prostate cancer. Since then, we have regularly examined it when IVL was suspected to investigate usefulness of PAP as a diagnostic marker for IVL. We retrospectively evaluated usefulness of PAP as diagnostic marker of IVL. Design and methods: We reviewed clinical courses of 5 patients with IVL (3 males, 2 females) in comparison with 23 controls with hematologic malignancies other than IVL. Results: Serum levels of PAP were elevated in all of the 5 patients with IVL and 2 of the 23 controls. The difference was statistically significant using a chi-square test \( (p=0.0002) \). Sensitivity and specificity of PAP were 100% and 91%, respectively, in the diagnosis of IVL. Its serum levels were closely associated with disease status. Interpretation and conclusions: This study suggests that PAP might be a useful marker for the screening and assessment of disease activity and responses to the treatment of IVL.

Figure 1. Serum levels of PAP in IVL and other hematologic disease patients. Large spot shows median.

Figure 2. Clinical course of Case 3. Serum levels of PAP were associated with those of LDH and sIL-2R.

Figure 3. Clinical course of Case 5. Serum levels of PAP were associated with those of LDH.

Intravascular large B-cell lymphoma (IVL) is characterized by distribution of lymphoma cells predominantly or exclusively within the blood vessels. The clinical aspects of its presentation are puzzling, and it is difficult to unify into a single disease process. The classic presentation occurs in middle- or old-aged patients with a macular or papular rash and neurologic symptoms. Lymphadenopathy is rare, and fever, generalized weakness, and weight loss are frequent manifestations. IVL has another subtype, an Asian variant, which is characterized by hemophagocytic syndrome (HPS), pancytopenia, hepatosplenomegaly, and bone marrow involvement. It usually lacks any neurological or skin abnormalities, which are typical features of classical IVL. Bone marrow examination is a useful method for making definitive diagnosis. Without early diagnosis, the disease typically pursues aggressive and often fatal courses.

IVL has been treated as fever of unknown origin (FUO), and many patients have been treated inadequately based on incorrect diagnoses. A 52 year-old male with FUO was admitted to Toranomon Hospital in 1987 (Case 1). Neither infections nor collagen diseases were probable causes of FUO. Physical and radiological examination did not show any evidence of malignant diseases. We determined serum levels of prostatic acid phosphatase (PAP) for the screening of prostate cancer. They were elevated to 4.7 µg/L (normal range <3.0 µg/L). Diagnosis of IVL was established at postmortem examination, and prostate cancer was denied. This case suggests a possible association between IVL and PAP.

PAP is a subtype of acid phosphatase. Four forms of acid phosphatase isoenzymes exist at the structural level of genes. The erythrocytic and lysosomal forms are expressed in most cells, whereas, the prostatic and
macrophagic forms have a more limited expression. Thus, the prostatic form (PAP) is specific for neoplasms originating from the prostate gland. PAP had been the main biochemical diagnostic test for prostate cancer until the arrival of prostate-specific antigen (PSA). Since 1987, measurement of PAP was incorporated into evaluation of FUO in Toranomon Hospital. We will describe the clinical course of 5 patients with IVL, in whom serum levels of PAP were determined.

**Patients and methods**

**Patients**

Five patients with pathology-proven IVL including Case 1 were admitted to our hospital between 1987 and 2002. Their clinical characteristics are shown in Table 1. No patients were diagnosed with HPS, while serum levels of ferritin, a marker of HPS, were elevated in all of the 5 patients. No patients were pancytopenic, while all of the patients remained febrile at the diagnosis of IVL.

**Measurement of serum levels of PAP**

Serum levels of PAP were determined using a commercial kit (DPC immobilite PAP, Diagnostic Products Co., CA). This kit does not cross-react with prostate specific antigens (PSA). Normal range of serum PAP is 0.2-3.0 ng/mL. Serum levels of PAP were measured serially in 2 patients, and once at the time of IVL diagnosis in the other 3 patients. To evaluate destruction of the prostate, serum levels of PAP were determined in 2 patients (Cases 2 and 3).

We measured them in 23 patients with hematologic diseases other than IVL to evaluate specificity of PAP in making a diagnosis of IVL. They included acute myeloid leukemia (n=6), acute lymphoid leukemia (n=1), mantle cell lymphoma (n=1), follicular lymphoma (n=4), diffuse large B-cell lymphoma (n=3), Burkitt lymphoma (n=1), NK/T-cell lymphoma (n=2), Hodgkin lymphoma (n=1), multiple myeloma (n=2), adult T-cell leukemia/lymphoma (n=1), aplastic anemia (n=1). Twenty were male, and three were female. Median age was 54 years (range, 16-72). Diagnosis of HPS was not established in any of these 23 patients. Since prostatic glands were not pathologically evaluated in any of the 23 patients, it remained unknown whether the prostate was involved by malignant cells.

**Results**

Serum levels of PAP were elevated in all of the 5 patients with IVL and 2 of the 23 controls (Figure 1). The difference was statistically significant using a chi-square test (p=0.0002). Sensitivity and specificity of PAP were 100% and 91%, respectively, in the diagnosis of IVL. Serum levels of PSA remained normal in 2 patients, 0.6 μg/L and 0.1 μg/L respectively (Cases 2 and 3). The clinical courses of Case 3 and 5 are shown in Figure 2 and 3. Serum levels of PAP were associated with those of LDH or soluble IL-2 receptors (sIL-2R) and with disease status. The patient of case 5 died of invasive aspergillosis, while IVL remained in remission. Serum levels of PAP remained normal, while those of sIL-2R and LDH were elevated.

Autopsy was approved in 4 patients (2 males and 2 females), and the other patient received biopsy of the prostate. The involved organs by IVL cells are shown in Table 1. All the three male patients showed hyperplasia of the prostate, but prostate cancer was not found in any of these patients. Pathological findings of the prostate were as follow: proliferation of lymphoma cells within the lumina of small vessels (Case 1), infiltration of lymphoma cells in the interstitial tissue (Case 2), and infiltration of lymphoma cells into the capillary and small vessels in the interstitial tissue (Case 3). These patients’ prostate glands were damaged severely by infiltration of IVL cells into the small vessels of the interstitial tissues of the prostate.

**Discussion**

There are three possibilities in interpreting the results of this study. The first hypothesis is that IVL cells produce PAP, and that elevation of its serum concentration might reflect the tumor burden. However, our colleagues reported that immunohistochemical examination of IVL cells was negative for PAP, and this possibility seems unlikely.

The second possibility is that serum concentration of PAP might be elevated due to release of PAP or its cross-reactants from necrotic tissue which is thrombosed by massive lymphoma cell growth or fibrin deposition. Lysoosomal acid phosphatase (LAP), a transmembrane protein expressed in almost all tissues, has been identified as cross-reactant of PAP, and Lin et al. reported that some acid phosphatases in the spleen and lung share at least one common antigenic epitope with PAP. LAP is expressed ubiquitously, and PAP is expressed in some malignant and non-malignant non-prostate tissues. IVL is associated with highly aggressive clinical courses, and it frequently embolizes the microvessels, causing severe tissue damages. These findings suggest that elevation of PAP concentration might reflect the tissue damages caused by IVL.

The other possibility is some cross-reactions with a macrophagic form of acid phosphatase. IVL is occasionally complicated with HPS in our country, in which macrophages are activated frequently. Patients with HPS were not included in the control group, and association between PAP and HPS was not examined in this study. Although diagnosis of HPS was not established in any of the 5 cases, we cannot neglect the possibility, and this issue awaits further investigation.

This study suggests that PAP might be a useful marker for the screening and assessment of disease activity and responses to the treatment of IVL. However, this study is too small to make a definite conclusion on the association between IVL and PAP. It is interesting that serum levels of PAP remain normal in most hematologic malignancies other than IVL. We speculated that tumor embolism rarely occurs in most hematologic malignancies, in which tissue damages are usually mild, leading to less frequent release of PAP and LAP into circulation.

Yukiko Kishi*1  Masahiro Kami*1  Eiji Kusuami†  Tomoka Mineyama†  Daitsuke Kato†  Tamea Hamabu†  Shigesaburo Miyakoshi†  Shin-ichi Morinaga†  Yoshitomo Muto†  Shuichi Taniguchi†

*Department of Hematology, Toranomon Hospital, Tokyo, Japan.
†Haematopoietic Stem Cell Transplantation Unit, the National Cancer Center Hospital, Tokyo, Japan.

*Correspondence: Masahiro Kami, MD
Haematopoietic Stem Cell Transplantation Unit, the National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.
Tel: +81-3-3542-2511, Fax: +81-3-3542-3815,
E-mail: mkmami@ncc.go.jp

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