

Case Study

Elevated Plasma Fibrinogen in Clinically Asymptomatic Unicentric Castleman's Disease: A Case Report

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This is the first report of an early association between elevated fibrinogen and asymptomatic unicentric Castleman's disease (CD). A 49-year-old asymptomatic female who was serving as a normal control in an unrelated study was incidentally found to have significantly elevated levels of plasma fibrinogen. Upon further investigation with computer tomography scans and magnetic resonance imaging, the woman was found to have a mobile mass in the abdominal region which was surgically removed. Based on histological analysis, a diagnosis of CD was made. At four-month follow-up, no additional signs of CD were present and fibrinogen levels returned to the normal range. This report, therefore, signifies the importance for physicians to consider unicentric CD in the differential diagnosis when patients present with elevated levels of plasma fibrinogen. Awareness of this diagnostic possibility may lead to increased early diagnosis of CD before symptoms become apparent, and provide a marker candidate for CD activity that may assist in monitoring treatment success. [*J Clin Exp Hematop* 54(1): 85-88, 2014]

Keywords: Castleman's disease, fibrinogen, early diagnosis, incidental findings

INTRODUCTION

Plasma fibrinogen is the primary coagulation protein involved in the process of clotting as well as an important determinant of blood viscosity and platelet aggregation.^{1,2} Elevated plasma fibrinogen levels are associated with a wide range of vascular and non-vascular diseases including neoplasia.³ Castleman's disease (CD) is a rare non-clonal lymphoproliferative disorder of unknown etiology⁴ accompanied by a systemic inflammatory response linked with an overt production of interleukin-6.⁵ Patients with CD may present with a variety of symptoms, which depend on tumor

size and the site of involvement. These may also manifest in compressive symptoms. For abdominal locations, clinical symptoms typically have a late onset due to an important size of the tumor. In this report, a case of asymptomatic unicentric abdominal CD is presented. This case was discovered incidentally due to elevation of plasma fibrinogen in a healthy individual, who was serving as a control in a clinical experiment.

CASE REPORT

As part of a series of experiments, which were intended to clarify the mechanism of the hemostatic effect of gallium nitrate in wounds,⁶ plasma fibrinogen levels were quantified before and after addition of gallium nitrate. A 49-year-old female, a previously healthy physician who provided blood samples for the experiments, was found to have significantly elevated plasma fibrinogen levels. She was asymptomatic, a non-smoker, and performed regular physical exercise. Her initial plasma fibrinogen level was 6.3 g/L (normal range 1.5–3.5 g/L), but six weeks later had risen to 7.3 g/L. The majority of laboratory findings were within normal ranges with the exception of inflammation markers: fibrinogen 7.3 g/L, C-reactive protein 28 mg/L (normal < 6 mg/L), and erythrocyte sedimentation rate 43 mm (normal range 7–15 mm). Her iron status flanked the reference intervals: serum iron 33 µg/dL (normal range 33–193 µg/dL), transferrin 2.1 g/L (normal range 2.0–3.6 g/L); total iron binding capacity

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was 293 µg/dL (normal range 250–350 µg/dL). A slightly increased serum level of IgG was observed (16.1 g/L as compared to normal values of < 14 g/L), whereas IgG4 levels were within normal range, and the anti-nuclear antibodies were positive at 1/640. No abnormalities for blood count were found. Viral serologies were negative for human immunodeficiency virus and human herpesvirus 8. Tumor markers were not elevated (α -fetoprotein, carcinoembryonic antigen, CA 19-9, CA 15-3, neuron specific enolase), and physical evaluation including abdominal palpation were considered normal.

Computed tomography (CT) scans of the abdomen revealed a homogeneous 3 × 3 cm mobile mass surrounded by three small nodules with no involvement of adjacent organs. An initial CT scan indicated that the mass was located on the right side of the sus-mesocolic area (Fig. 1A). One month later, a second CT scan indicated that the mass was on the left side of the abdomen (Fig. 1B). Magnetic resonance imaging (T2-weighted images) further detected a homogeneous hyperintense contrast enhancing mass lesion of 3 cm length located below the antrum. The mass displayed homogeneous contrast enhancement after intravenous gadolinium injection (Fig. 2). Evaluation with combined fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) confirmed increased metabolic activity that was localized to the mass with no intra- or extra-abdominal extension. Needle core biopsy was not deemed feasible because of the mobility of the mass.

The patient underwent abdominal laparoscopic exploration which revealed a solid pediculated mass surrounded by several adenopathies located in the right upper part of the omentum below the gastric pylorus, the largest measuring 3 cm in size. The tumor was completely resected and presented as a sharply demarcated lesion (Fig. 3).

Microscopically, the nodules corresponded to enlarged lymph nodes which retained normal architecture. The germinal centers varied in size and were located throughout the lymph node parenchyma. Some germinal centers were hyperplastic whereas others were depleted of lymphocytes and contained hyalinized capillaries (Fig. 4). The arrangement of mantle zone lymphocytes in concentric layers led to an “onion skin” appearance of the follicles. The interfollicular zone was characterized by sheets of proliferating mature and polytypic plasma cells (Fig. 5). The sinuses were unapparent. The final diagnosis was mixed, hyaline vascular and plasmacytic type CD.

Following surgery, the patient recovered well and was discharged four days after surgery. At four months follow up, the patient was in good clinical condition. In addition, plasma fibrinogen, C-reactive protein and serum levels of IgG had returned to normal values. The positivity of the anti-nuclear antibodies decreased and a new FDG-PET/CT scan was negative for indications of disease.

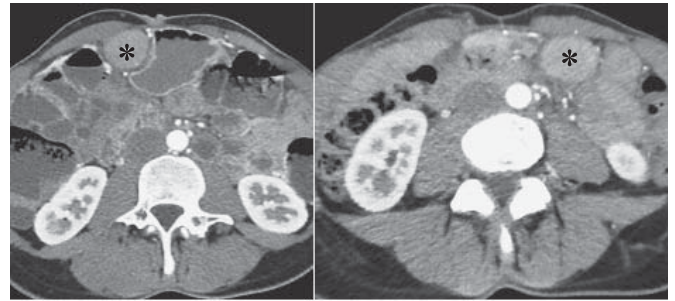


Fig. 1A (left image)/ **1B** (right image). Abdominal computed tomography scan showing a mobile mass (*) first in the right abdomen (1A) and then in a second exam in the left abdomen (1B).



Fig. 2. Homogeneous mass (*) on T2-weighted magnetic resonance imaging.

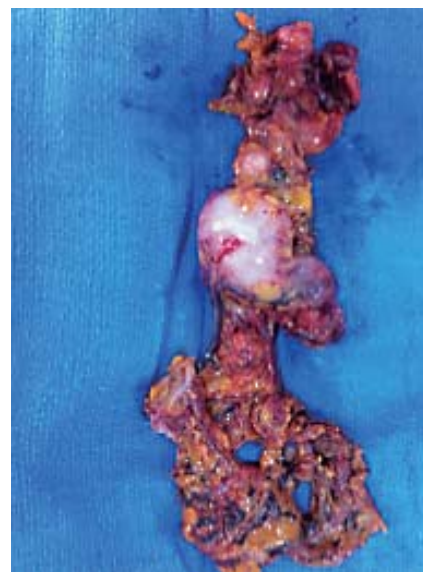


Fig. 3. Resected specimen of Castleman disease in the omentum. The main nodule is surrounded by several adenopathies.

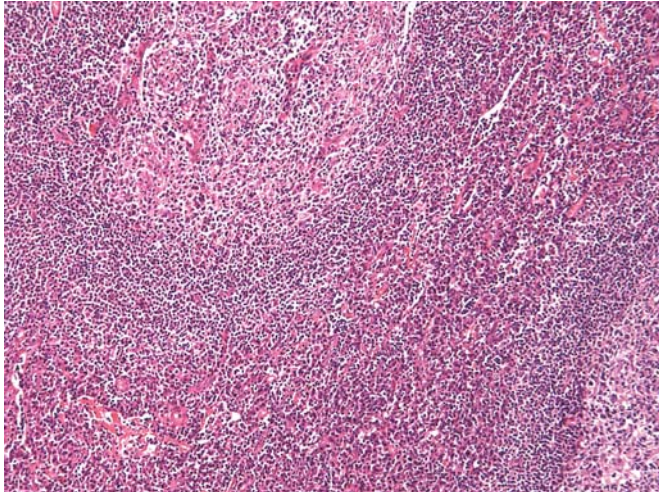


Fig. 4. Partial depletion of lymphocytes and penetration of hyalinized capillaries in some germinal centers. H&E stain, × 100.

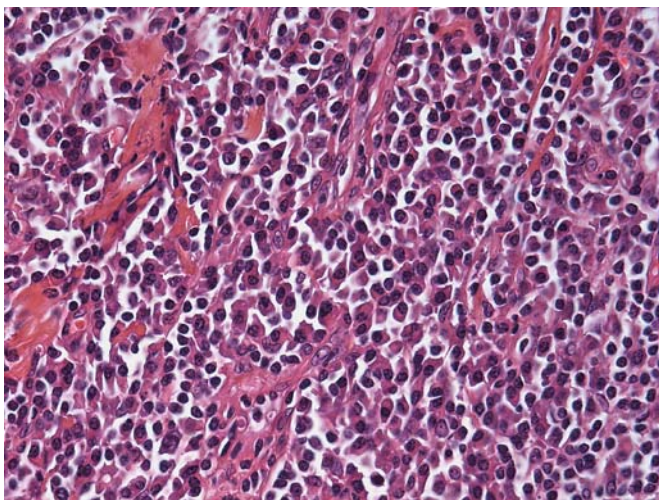


Fig. 5. Interfollicular expansion of mature plasma cells. H&E stain, × 200.

Notably, written informed consent was obtained from the patient for publication of this case report and all accompanying images.

DISCUSSION

Limited knowledge exists regarding the disease etiology and the non-specific presenting symptoms of CD. Diagnosis remains a challenge and is currently based solely on the histopathologic evaluation of lymph nodes. This case appears to be the first report of asymptomatic unicentric CD associated with elevated fibrinogen. This case may shed light on the role of fibrinogen in histological variants of CD, as well as in early detection and post-treatment assessment of CD.

To date, three histological variants of CD have been described (hyaline vascular, plasmacytic, and mixed cellularity types) and two clinical presentations are also defined (unicentric and multicentric). The hyaline-vascular variant is the predominant form (90% of CD cases)⁷ generally seen in localized subtypes, and is often curable with surgery. Plasma-cell type is less common (10% of CD) and associated with systemic manifestations, such as fever, anemia, hyper- γ -globulinemia, and an increase in acute phase proteins.⁵ In our case, the patient presented with a mixed CD type, which was characterized by the presence of hyaline vascular CD and plasmacytic CD.⁸ Some authors have hypothesized that the plasma cell type represents an earlier, more active stage of the disease process, and the hyaline-vascular type represents a later, less active stage.⁹ The presented case may support this hypothesis, as fibrinogen was significantly elevated when the tumor was only 3 cm, the patient had no sign of chronic inflammatory syndrome, and there was no evidence, in particular, of iron deficiency anemia.

Further highlighting the potential role of fibrinogen in CD was the asymptomatic presentation of this case. In the review of CD provided by Bowne *et al.*,⁹ tumor sizes of abdominal and retroperitoneal location were described as varying from 5 to 15 cm; only retroperitoneal tumors (developed in an enclosed space, so more rapidly symptomatic) or large pelvic masses (20 × 15 cm) were responsible for digestive symptoms or back pain. Small mesenteric tumors (5 and 7 cm) were discovered from abnormal lab findings (elevated erythrocyte sedimentation rate, anemia, interleukin-6) or systemic symptoms (myalgia, arthralgia, paresthesia).⁹ In contrast, the patient in this case study was entirely asymptomatic with no suspicion of any clinical condition possibly associated with elevated fibrinogen such as metabolic syndrome¹⁰ or low physical activity.^{11,12} Thus, plasma fibrinogen was instrumental in detecting the CD at a very early stage. Moreover, the fibrinogen level correlated with disease activity; it appeared to increase rapidly during the early stage of disease, and decreased soon after surgical resection.

This case report indicates that, upon finding elevated levels of fibrinogen in the blood, clinicians should consider unicentric CD in the differential diagnosis. This may lead to early diagnosis before symptoms become apparent. Additionally, plasma fibrinogen levels may also serve as a surrogate marker of successful treatment. In light of the simple and inexpensive testing available for plasma fibrinogen levels, further testing and research appears both warranted and highly feasible.

CONFLICT OF INTEREST ACKNOWLEDGEMENTS

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