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CASE REPORT

Confirmed Cryoglobulinemia and Hyperviscosity Syndrome Secondary to Multiple Myeloma-IgA Kappa from Routine Blood Test: a Case Report

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SUMMARY

Background: **Cryoglobulins and hyperviscosity syndrome (HS) sometimes occur in multiple myeloma (MM), which are considered clinical emergencies. In laboratory practice, aspiration failure in routine blood tests sometimes occurs when the sample is inadequate. Here, a case of cryoglobulinemia and HS associated with advanced multiple myeloma was reported, which unusually is initially confirmed by aspiration failure in a routine blood test with sufficient sample.**
Methods: **A case of a 48-year-old female whose diagnosis of cryoglobulinemia and hyperviscosity syndrome secondary to MM-IgA kappa was confirmed from routine blood test.**
Results: **The sufficient sample for routine blood test could not be analyzed in a hematology analyzer due to aspiration failure, which was found to be caused by high viscosity and poor liquidity. A peripheral blood smear showed numerous non-cellular clouds, erythrocyte rouleaux formation, and plasma cell infiltration. After a water bath, the non-cellular clouds evidently disappeared, and the routine blood test was successfully conducted. Centrifugation of the sample for biochemical test, which had previously failed, was also possible. The case was confirmed as complications of cryoglobulinemia and HS associated with advanced MM, and the non-cellular clouds were identified as cryoglobulins.**
Conclusions: **This case report provides an effective way for clinicians to deal with this kind of abnormal sample and limited but important laboratory evidence to establish early diagnosis of cryoglobulinemia and HS secondary to MM.**
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KEY WORDS

multiple myeloma, routine blood test, cryoglobulinemia, hyperviscosity syndrome

INTRODUCTION

Multiple myeloma (MM) is a malignant monoclonal plasma cell disease, which accounts for 18% of hematological malignancies in the United States [1]. Incidence of MM increases with age; median age at diagnosis is 69 years [2]. Almost all patients with MM will experience relapse during complete remission, despite the de-

velopment of novel therapies [3]. Our case was also an advanced multiple myeloma, at a relatively young age of 48.

Cryoglobulins are detected in a wide variety of diseases and MM accounts for 6 - 10% of patients with cryoglobulinemia [4], which tend to precipitate with cold temperature and dissolve with rewarming [5]. Cryoglobulinemia is mainly characterized by cutaneous manifesttation in almost half of the patients [5].

Hyperviscosity syndrome (HS) occurs especially in advanced cases of MM [6]. HS is characterized by altered blood flow properties [7], which cause a cluster of manifestations that include mucosal bleeding, visual impairment, and neurological symptoms. Other nonspecific constitutional symptoms include malaise, fatigue, and shortness of breath [8].

Cryoglobulinemia and hyperviscosity syndrome (HS) associated with MM are considered clinical emergencies and diagnosed mainly by clinical presentation and laboratory results. Delayed diagnosis can lead to severe organ damage and even endanger patients' lives [9]. Aspiration failure in inadequate samples for routine blood tests is a bit of a common phenomenon that usually occurs due to some compromising factors in laboratory practice. Here, we report a case of cryoglobulinemia and HS associated with advanced MM. Interestingly, the diagnosis of these two complications secondary to MM was first confirmed by aspiration failure in a sufficient sample for routine blood test.

CASE PRESENTATION

Accidental laboratory findings

Several tubes of blood collected from a 48-year-old female patient in the Department of Hematology were sent to our laboratory in December 2018, and one sample was analyzed in a Coulter LH 750 automated hematology analyzer (Beckman Coulter, Brea, CA, USA) for blood routine test. An alarm was raised when aspiration failure occurred which referred to the sample being insufficient. After we checked the sample, we realized it may not be the same case as that given above, because there was still enough blood remaining to be aspirated for the automated mode.

The sample was found to have high viscosity and poor liquidity. These abnormal properties made it difficult to create a standard smear from the sample. The peripheral blood smear showed numerous non-cellular clouds, which surprised us even more (Figure 1). We decided to put the sample in a 37°C water bath for 30 minutes. The warm bath alleviated the high viscosity and poor liquidity, and the sample was re-analyzed successfully in the LH 750. We then repeated the smear to recheck the strange amorphous clouds. The smear showed severe normocytic anemia, abnormal plasma cell infiltration (4%), obvious erythrocyte rouleaux formation, and most of the non-cellular clouds had obviously disappeared. Meanwhile, a problem occurred with the biochemical-test sample in that enough serum could not be obtained after 2 runs of routine centrifugation (1,610 g, 10 minutes). A water bath at 37°C for 15 minutes greatly improved centrifugation as well (Figure 2).

Clinical manifestations and medical history

The patient had been diagnosed as MM (IgA kappa; ISS III) according to International Staging System (ISS) in June 2017, mainly based on these results: detection of total Ig levels revealed an evident increase of IgA to 5,660 mg/dL (reference intervals 82 - 453) accompanied with an increase of κ free light chain (FLC) of 1,539.8 mg/dL (reference intervals 629 - 1,350); A bone marrow biopsy hinted approximately 93.2% atypical plasma cell infiltration. Response was good to 1 cycle of chemotherapy and follow-up maintenance therapy. In December 2018, the patient was admitted to the Department of Hematology in our hospital for a chief complaint of 1-year history of general fatigability and headache, which had been aggravated in the last month. Other clinical manifestations were anemia symptoms: generalized weakness, poor appetite, palpitation worsened with any movement; and a cluster of predominant symptoms such as spontaneous epistaxis, gingival bleeding, and tinnitus. Based on the above clinical manifestations and laboratory findings, complications of cryoglobulinemia and concurrent HS secondary to IgA kappa MM was diagnosed. After imposition of urgent measures to reduce blood viscosity, the patient's clinical condition greatly improved.

DISCUSSION

This is the first case report of cryoglobulinemia and concurrent HS secondary to IgA kappa MM confirmed by accidental findings in a blood routine test. Aspiration failure in an abundant sample for routine blood tests is a relatively rare and abnormal phenomenon. Later discoveries all stemmed from this anomaly. The amorphous non-cellular clouds on the peripheral blood smear were suspected to be cryoglobulin aggregates, which was confirmed based on the following evidence: alleviation of high viscosity and poor liquidity of the sample after water bath; disappearance of non-cellular clouds on the smear after water bath; the answers were found when consulting the literature. Based on literature review, there have been only 3 publications so far that have reported cryoglobulin figures [10-12]. Two of them also showed another image evidence of cryoglobulins on blood films, namely, multiple basophilic inclusion bodies in neutrophils [10,11], which were not observed in our case. The cold-induced cryoglobulin aggregates were suggested to have contributed to HS. Diagnosis of HS was based on the following aspects: the properties of high viscosity and poor liquidity in the sample, the typical neurological presentation (headache and tinnitus), and mucosal bleeding (spontaneous epistaxis, gingival bleeding). HS was supposed to lead to aspiration

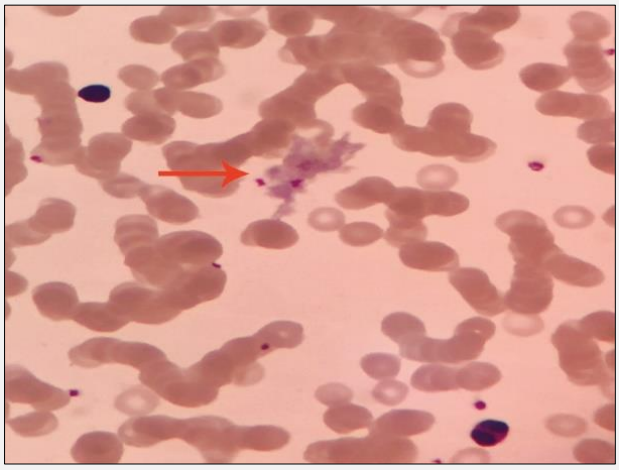

Figure 1. The peripheral blood smear showed numerous cloud-shaped non-cellular components (Wright-Giemsa stain, x 1,000).

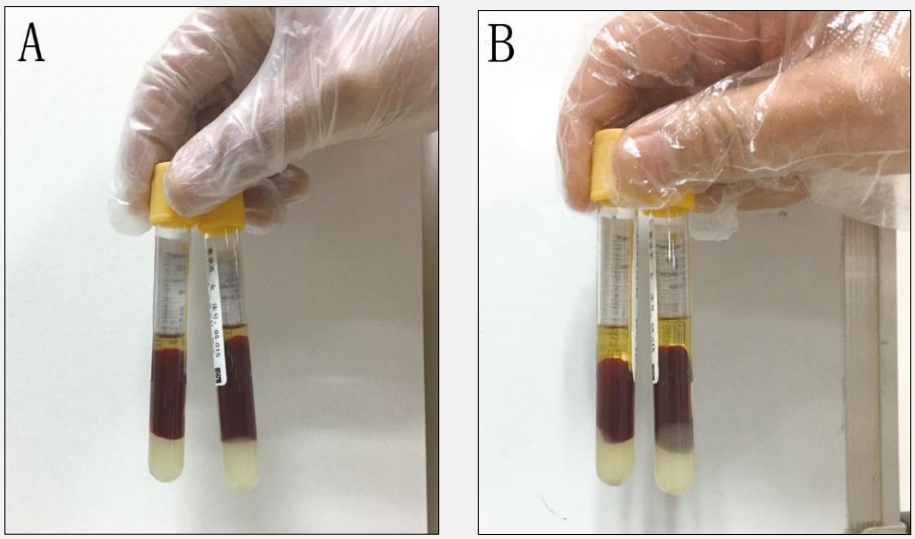

Figure 2. The sample for the biochemical test, centrifuged before (A) and after (B) a 37°C water bath for 15 minutes.

failure in routine blood test and centrifugation failure in biochemical-test sample. MM was later confirmed as the underlying etiology in our case. The lesson to be learned is that more serum can be obtained if centrifugation occurs after a water bath at 37°C for 30 minutes, not for only 15 minutes. A similar case of centrifugal failure due to hyperviscosity in an advanced case of myeloma has also been reported [6].

MM associated with either HS [7,8,13] or cryoglobulinemia [5,9,10] is sporadically reported in the literature. Our case of IgA kappa MM simultaneously associated with cryoglobulinemia and HS is thought to be relative-

ly rare; interestingly, it is the first report of these 2 complications being initially diagnosed from aspiration failure in a routine blood test. The series of accidental laboratory findings raised suspicion of cryoglobulinemia and HS and therefore lead to timely diagnosis and treatment. The limitations of this report are that plasma viscosity was not measured and no cryoglobulin precipitation experiment was conducted due to equipment constraints and lack of preparation for relevant knowledge.

CONCLUSION

We confirmed a case of cryoglobulinemia and concurrent HS associated with IgA kappa MM, starting with an adequate sample for the routine blood test that prompted a warning of aspiration failure in an LH 750 analyzer. A series of laboratory findings of this abnormality was also described. This case emphasizes the importance of inspecting possible etiologies of uncommon samples and of paying attention to diagnostic clues in complicated cases in laboratory experience.

Declaration of Interest:
The authors declare that they have no competing interests.

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