Immunoglobulin D-λ/λ biclonal multiple myeloma: A case report

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**Abstract**

**BACKGROUND**

Immunoglobulin D (IgD) multiple myeloma (MM) is a rare subtype of MM and commonly occurs in younger subjects but at a later stage of the International Staging System (ISS) when admitted. As a special type of IgD myeloma, IgD-λ/λ biclonal MM is rarer. Its serum protein electrophoresis and serum immunofixation electrophoresis (IFE) might find no anomalies even if the bone marrow (BM) examination is performed. Thus, it is easy to miss the diagnosis.

**CASE SUMMARY**

A 62-year-old man diagnosed as IgD-λ/λ myeloma (ISS stage III) was admitted with fatigue and weight loss. The physical examination suggested an anemic face, a few moist rales at the left lung base, and mild concave edema in both lower extremities. Laboratory examinations showed the elevated creatinine levels, β2-microglobulin, lactic dehydrogenase, and erythrocyte sedimentation rate, while the decreased neutrophils, granulocytes, and hemoglobin. In the serum protein electrophoresis, there appeared two inconspicuous M-spikes. Serum IFE indicated an over-representation of lambda light chain and yielded two monoclonal bands in λ region, but only one corresponding heavy chain band in the antisera to IgD region. The BM histology and BM cytology both supported the diagnosis of IgD-λ/λ myeloma.

**CONCLUSION**

This case highlights the differential clinical manifestations and laboratory findings of IgD-λ/λ myeloma to help minimize the chance of misdiagnosis.
A 62-year-old male farmer was hospitalized for fatigue and weight loss for more than 1 mo, without fever or bone pain. The peripheral blood examination in a local hospital indicated severe anemia with a hemoglobin level of 54 g/L and a potentially malignant tumor from the blood system. Therefore, he was admitted to Huaihe Hospital of Henan University.

**Core Tip:** Immunoglobulin D (IgD)-λ/λ myeloma is extremely rare and has a later International Staging System stage at diagnosis. The median survival time is shorter than that of other subtypes, and renal insufficiency is prone to occur at the time of diagnosis. Furthermore, the laboratory examination tends to consider IgD-λ/λ myeloma as other isotypes in that its serum immunofixation electrophoresis shows two bands in the λ region but no responding heavy chain band. Therefore, more complete serum immunofixation electrophoresis should be conducted to reduce the rate of missed diagnoses.

**INTRODUCTION**

Immunoglobulin (Ig) D multiple myeloma (MM) is a rare disease, accounting for 2.0% to 2.5% of all MM cases, but the incidence has presented an increasing tendency in recent years[4,5]. In addition to the typical clinical manifestation of “CRAB” (hypercalcemia, renal insufficiency, anemia, or bone lesions), IgD MM is frequently accompanied by infection, fatigue, weight loss, etc[2,3]. IgD MM is classified into two types, kappa (κ) and lambda (λ); the type λ occupies a dominant position and the IgD κ is rare[4]. The majority of MM are monoclonal; only precious few MM are biclonal, which almost all belong to the heavy chain type, such as IgG/IgA, IgG/IgM, and IgG/IgG[5]. Thus, the infrequent type of light chain biclonal MM, and the IgD-λ/λ biclonal MM, are extremely rare. At present, only a few cases have been reported[8,9].

Compared to the other subtypes of MM, IgD MM is often more common in younger individuals and has a higher incidence of renal failure, a more advanced stage by the international staging system (ISS), and a worse prognosis[9]. The laboratory examination frequently presents higher levels of creatinine concentration, lactic dehydrogenase (LDH), β2-microglobulin, and C-reactive protein (CRP) than other MM subtypes[6,7]. The M-spikes in serum electrophoresis is not obvious due to the low levels of serum IgD concentration[8,9]. Similarly, the serum protein electrophoresis of IgD-λ/λ MM shows two subtle M-spikes and two bands appear in the serum immunofixation electrophoresis (IFE). Then, combined with the identification of bone marrow (BM) histology, immunohistochemistry, and immunophenotype of myeloma cells, the patients could be diagnosed as IgD-λ/λ myeloma[10]. In view of the low levels of serum IgD content and that immune serum anti-IgD is not routinely used in many laboratories, the diagnosis of type IgD-λ/λ myeloma is prone to be missed or confused with a type of light chain myeloma or monoclonal myeloma[4,11].

In this paper, we report the clinical case of a patient with IgD-λ/λ MM, who presented overexpression of IgD λ and free light chain (FLCs) λ with two bands in serum IFE, in order to summarize the clinical features and laboratory examination to help clinicians enhance the early diagnosis of IgD-λ/λ.

**CASE PRESENTATION**

**Chief complaints**

Fatigue and weight loss for more than 1 mo.

**History of present illness**

A 62-year-old male farmer was hospitalized for fatigue and weight loss for more than 1 mo, without fever or bone pain. The peripheral blood examination in a local hospital indicated severe anemia with a hemoglobin level of 54 g/L and a potentially malignant tumor from the blood system. Therefore, he was admitted to Huaihe Hospital of Henan University.

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History of past illness
No particular previous medical history.

Personal and family history
The patient had no history of exposure to industrial poisons or radioactive substances, and was not smoking or drinking alcohol. The family history was unremarkable.

Physical examination
The patient presented an anemic face; the percussion of the lungs presented a little dullness, a few moist rales were heard at the left lung base, and mild concave edema was seen in both lower extremities.

Laboratory examinations
Laboratory evaluation at the Huaihe Hospital of Henan University showed a medium degree of anemia with a hemoglobin level of 61 g/L. Further blood examination indicated renal dysfunction and elevated erythrocyte sedimentation rate and N-terminal pro-brain natriuretic peptide (NT-PROBNP) (Table 1). The other laboratory findings, including blood coagulation functions, stool for routine, blood lipids, and blood sugar, were normal.

Serum protein electrophoresis on agarose gel suggested an elevation of α2-globulin and γ-globulin, and two slight M-spikes appeared and a band within the γ fraction (the other band within α2 fraction was obscure) was seen. To categorize the M protein, we conducted serum IFE, which consisted of antisera to IgA, IgM, IgG, κ, and λ, and the results yielded two monoclonal bands in the λ region without corresponding heavy chain bands, corresponding to the distinct elevation of serum λ FLC (Figure 1). Thus, we highly suspected the possibility of type IgD or IgE or FLC M protein component. Subsequently, we implemented a second serum IFE with antisera to IgD, IgE, κ, and λ. The results showed two monoclonal bands in antisera to λ but only one corresponding heavy chain band in antisera to IgD, which indicated a diagnosis of IgD-λ/λ myeloma by correlating the clinical manifestation and laboratory examinations.

BM cytomorphologic (anterior superior spine) examination found a marked increment of plasma cells, mainly immature plasma cells, which accounted for 82% of the BM nucleated cells (Figure 2). Flow cytometry suggested positivity of monoclonal plasma cells (70.12% of total nucleated red blood cells) with the following immunophenotype: CD38, cytoplasmic lambda, and CD229. All of the monoclonal plasma cells expressed CD229, CD38, and cytoplasmic lambda and partly expressed CD138 (Figure 3). Undoubtedly, BM cytomorphologic examination and flow cytometry supported the diagnosis of plasma cell myeloma. Furthermore, analysis of chromosome karyotype was as follows: 46,XY;46,Yt(X;4)(p11.2;q21), no abnormal cloning. Gene analysis of the blood tumor mutant group was mainly normal.

Combined with the clinical, and laboratory data above, the patient was diagnosed with stage ISS III myeloma.

FINAL DIAGNOSIS
IgD-λ/λ MM with renal failure (late stage of uremia).

TREATMENT
The patient was treated with BCD chemotherapy (bortezomib plus cyclophosphamide and dexamethasone) for approximately two cycles. The specific method of drug use was as follows: Bortezomib: 1.3 mg/(m²·d) mixed in 0.9% sodium chloride injection (1 mL), which was given subcutaneously on the 1st, 4th, 8th, and 11th days; cyclophosphamide: 300 mg/(m²·d), intravenous (IV) injection on the 1st, 4th, 8th, and 11th days; and dexamethasone: 20 mg/d, IV, on the 1st, 2nd, 4th, 5th, 8th, 9th, 11th, and 12th days. Partially confined to the patient’s finances, later rounds of chemotherapy were not performed consistently.

For the anemic condition, treatment with blood transfusions (suspended red blood cells with white blood cells removed) was given many times.

As for the renal failure, given the influence of hemodialytic treatment on the patient, symptomatic treatment, such as lowering creatine and protecting renal function, was
# Table 1 Laboratory data in hospital

| Item                                                                 | Result  | Reference range         |
|----------------------------------------------------------------------|---------|-------------------------|
| **Peripheral blood**                                                 |         |                         |
| White blood cells (× 10^9/L)                                          | 4.30    | 4-10                    |
| Neutrophils (× 10^9/L)                                               | 2.89    | 3.5-5.5                 |
| Red blood cells (× 10^{12}/L)                                        | 1.81    | 4.0-5.5                 |
| Hemoglobin (g/L)                                                     | 61      | 120-160                 |
| Erythrocyte sedimentation rate (mm/1^{st} h)                         | 150     | 0-20                    |
| **Anemia project**                                                   |         |                         |
| Folic acid (ng/mL)                                                   | 4.9     | ≥ 6.59                  |
| Vitamin B\(_12\) (pg/mL)                                            | 320.00  | 180.00-900.00           |
| Ferritin (ng/mL)                                                     | 636.60  | 11.00-306.8             |
| **Urine analysis**                                                   |         |                         |
| Urine protein                                                        | +       | -                       |
| Urine sugar                                                          | -       | -                       |
| White blood cells                                                    | +       | -                       |
| Blood                                                                | -       | -                       |
| Urinary sediment                                                     | Normal  |                         |
| **Biochemistry**                                                     |         |                         |
| Aspartate aminotransferase (U/L)                                     | 28      | 8-40                    |
| Alanine aminotransferase (U/L)                                       | 12      | 0-40                    |
| Alkaline phosphatase (U/L)                                           | 50      | 40-100                  |
| Blood urea nitrogen (mmol/L)                                         | 23.97   | 2.9-8.2                 |
| Creatinine (μmol/L)                                                  | 874     | 35-80                   |
| Uric acid (μmol/L)                                                   | 732     | 155-357                 |
| Albumin (g/L)                                                        | 32.5    | 34-48                   |
| Total protein (g/L)                                                  | 63      | 60-80                   |
| Lactate dehydrogenase (U/L)                                          | 148     | 109-245                 |
| N-terminal pro-brain natriuretic peptide (pg/mL)                     | 9670.00 | 0-125                   |
| C-reactive protein (mg/L)                                            | 4.1     | 0-8.2                   |
| Ca (mmol/L)                                                          | 2.27    | 2.0-2.5                 |
| P (mmol/L)                                                           | 1.84    | 0.9-1.34                |
| Fe (μmol/L)                                                          | 17.4    | 11-30                   |
| **Serological test**                                                 |         |                         |
| β2-microglobulin (μg/mL)                                             | > 13.77 | 0.9-2.7                 |
| IgM (mg/dL)                                                          | 5.55    | 46-304                  |
| IgA (mg/dL)                                                          | < 6.67  | 82-453                  |
| IgG (mg/dL)                                                          | 264.00  | 751-1560                |
| LC (mg/dL)                                                           | 134.00  | 629-1350                |
| λ-LC (mg/dL)                                                         | 1910.00 | 313-723                 |

Ig: Immunoglobulin; LC: Light chain.
used; however, the effect was minimal.

**OUTCOME AND FOLLOW-UP**

At the last follow-up, 5 mo after discharge, the anemic condition had been improved significantly, and the patient was free from the symptom of fatigue, but his renal function continued to deteriorate. Unfortunately, the patient died from a lung infection in the ensuing 2 mo. In this case, the median survival period for the patient with MM (ISS III) tended to be shorter than that for those with the other subtypes of myeloma, which is consistent with most studies[3,8,10].

**DISCUSSION**

MM is a malignant tumor characterized by BM infiltration of clonal plasma cells[3]. The abnormal immunoglobulin appears in circulation and can cause damage to related organs or tissues by monoclonal immunoglobulins or their fragments[3]. Hematological examination tends to find anemia, hypercalcemia, elevated β2-microglobulin and LDH, and decreased neutrophils, granulocytes, and hemoglobin[3]. In addition, the superfluous monoclonal protein frequently appears in circulation[3]. Therefore, the serum protein electrophoresis and serum IFE can provide strong evidence for classification of myeloma after the diagnosis of MM via BM histology, immunohistochemistry, and immunophenotype[3].

For IgD myeloma, the laboratory examination frequently presents higher levels of creatinine concentration, LDH, β2-microglobulin, and CRP than all other subtypes[3]. Theoretically, two ‘spikes’ could appear in the serum protein electrophoresis and two bands correspondingly appear in the serum IFE[11,12]. Nevertheless, generally it could not be seen due to the low levels of serum IgD[13]. In view of the infrequency of IgD myeloma, most hospitals or laboratories do not set the antisera to IgD as standard diagnostic items of serum IFE[11,12]. Moreover, the concentration of IgD is very low, even for IgD myeloma, and the elevation of monoclonal immunoglobulin in serum is so slight that it results in no visible M band and an inconspicuous monoclonal spike on serum electrophoresis[11,12]. Thus, the diagnosis of type IgD-λ/λ myeloma is apt to be missed or confused with light chain myeloma or monoclonal myeloma.

As in this patient, the ALB (32.5 g/L) decreased slightly, and TP (63.0 g/L) and globulin were within the normal range. The concentrations of IgM, IgA, IgG, IgE, and κ-LC were decreased in the serum IFE while IgD and λ-LC were significantly increased, but the corresponding M peak of serum protein electrophoresis was not visible, which is apt to be missed or misdiagnosed as light chain type MM. To improve the diagnostic level of IgD myeloma, the IgD examination is supposed to be included in the item of serum IFE for patients with MM. In light of the additional costs, the antisera to IgD can be applied when the subject is highly suspected to have MM, but there is no significant abnormality in the serum protein electrophoresis and routine IFE. Moreover, the laboratory examinations should be combined with the clinical manifestations and other examinational findings, such as BM cytology or BM biopsy.

Owing to the infrequency of IgD-λ/λ myeloma mentioned previously[11], its misdiagnosis rate is high. Thus, it is necessary to perform a full set of IFE when two bands in FLC fraction are found but no corresponding heavy chain is present. Consistently, there have been several studies[10,12] suggesting that the antisera to IgD IFE should be included in the routine diagnostic examination of myeloma in tertiary hospitals and medical laboratory centers.

As a first-line drug, bortezomib has been reported to prolong the survival time of patients with myeloma effectively[14]. One study has showed that the response to the bortezomib chemotherapy might be better in younger patients[14]. In addition, IgD MM is common in younger individuals, but the median duration of survival is shorter than in the other isotype[15,16], which indicates that the prognosis of patients with bortezomib chemotherapy might be more closely related to the type of MM than to the age of MM. In this case, the patient with IgD-λ/λ myeloma was alive for only 7 mo since showing symptoms, which might have been the result of the interrupted chemotherapy treatment or the even worse prognosis of double-clonal IgD myeloma than monoclonal IgD myeloma. We could guess that the double-clonal IgD myeloma might have a more aggressive course than monoclonal IgD myeloma and other isotypes. Of course, such a small sample was not tempting enough to support this inference. The specific reason remained unclear and needs further study. In view of the limited
Figure 1 Immunoglobulin D-λ/λ myeloma proteins detected by electrophoresis (France, Sebia, HYDRASYS). A: Serum protein electrophoresis showed two slight M-spikes that corresponded to alpha-2 and gamma globulins regions; B: Serum immuno-fixed electrophoresis [detected by anti-immunoglobulin (Ig) G, anti-IgA, anti-IgM, anti-κ, and anti-λ] presented two bands in anti-λ lane but no corresponding heavy chain band; C: Serum immuno-fixed electrophoresis (detected by anti-IgD, anti-IgE, anti-κ, and anti-λ) showed two M bands corresponding to IgD λ and free λ-light chains.

Figure 2 Bone marrow cytomorphologic examination (× 1000) showed a large number of immature plasma cells.

number of case reports on IgD-λ/λ myeloma worldwide, we present this case, hoping to provide a deeper understanding of the clinical features and laboratory findings of IgD-λ/λ myeloma, to increase the diagnosis rate in the same type of patients and to develop a more appropriate treatment plan.

CONCLUSION

In conclusion, the incidence of IgD myeloma is very low\(^1\), and compared to the other types of MM, besides the “CRAB” symptoms, the patients frequently have higher levels of creatinine, LDH, ß2-microglobulin, CRP content, and renal failure\(^2\). Moreover, a later disease stage with a more aggressive course of the disease, as well as younger age, have been noticed at diagnosis of IgD myeloma\(^3\). On the basis of identification of BM histology, immunohistochemistry and immunophenotype of
He QL. IgD-λ+λ myeloma

IgD-λ+λ myeloma cells, combined with serum protein electrophoresis and IFE, could be able to diagnose IgD myeloma\(^1\). However, the majority of laboratories have not established the immune serum anti-IgD as the general procedure\(^2\); thus, IgD-λ/λ myeloma is often misdiagnosed or neglected. To improve the diagnosis rate, this examination should be performed to exclude IgD-λ/λ myeloma when finding light chain myeloma while without any corresponding heavy chain. In addition, bortezomib is still an effective first-line treatment for IgD myeloma\(^3\); however, more appropriate drugs and treatments should be studied due to its worse treatment effect and prognosis than other isotypes.

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