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# Multiple Myeloma with Triclonal Gammopathy: case report and literature review

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***Abstract:***
*Triclonal gammopathy is a rare disease entity characterized by the presence of three populations of monoclonal immunoglobulins in the same patient. These three immunoglobulins can be of the same class, as shown by the observation we report in a 67-year-old patient whose triclonal IgA lambda gammopathy was observed in the context of multiple myeloma. As they can be of different classes as reported in the literature. The clinical and biological presentation of MM with triclonal gammopathy does not differ from that of MM with biclonal or monoclonal gammopathy. It also appears that the prognosis is not different, but this needs to be verified in large series. Although progress in the management of MM has led to long-term remissions, the number of relapses remains very high.*

***Key Words:*** *Triclonal gammopathy, Multiple myeloma, IgA, Lambda light chain, case report*

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## I. Introduction

Multiple myeloma (MM) or Kahler's disease is a primary malignant proliferation at the expense of B lymphocytes in the bone marrow. Morphologically, it is characterized by plasma cell infiltration of the marrow space and involvement of extraosseous tissue. Biologically, it is responsible for the production of monoclonal immunoglobulins and the presence of monoclonal proteins (light chains) in the plasma and/or urine [1]. It is the proliferation of a single clone of immunoglobulin-secreting cells that results in the secretion of a single homogeneous product (component M), revealed by a monoclonal peak. Rarely, a biclonal or triclonal gammopathy may be identified. Exaggerated proliferation of a group of cell clones, each of different genetic origin, may also be responsible for excessive and simultaneous production of a heterogeneous mixture of immunoglobulins that appears as a pluriclonal peak [2]. In patients with MM, the presence of biclonal gammopathy is relatively rare, accounting for 1-5% (3), while triclonal gammopathy is even more rare. We report a 69-year-old female patient with triclonal gammopathy of the lambda IgA type detected by the appearance of three bands in the gamma globulin fraction on serum protein electrophoresis whose immunoglobulin class was confirmed by serum immunofixation.

## II. Case Report:

The patient was 69 years old and complained of diffuse bone pain, anorexia and weight loss for six months associated with generalized weakness. Clinical examination revealed a patient in a wheelchair with edema of the lower limbs and an anemic syndrome. The blood count revealed a white blood cell count of 7.43 $10^3$/µL with a predominance of neutrophils (89.7%). Hemoglobin was 5.8 g/dL, MCHC 32.9 g/dL and MCV 90.0 fL and platelets 597.$10^3$/µL. The sedimentation rate was 165mm at the 1st hour. Regarding biochemical parameters, serum total protein level was 77 g/L, with profound hypoalbuminemia at 17.3 g/L. Renal failure was retained on urea at 1.00 g/L, and creatinine at 26.66 mg/L. Liver function tests were normal. Corrected serum calcium was 78.95 mg/dL. Urinalysis workup showed 24-hour proteinuria of 3.377 g/24h, albuminuria at 130.82mg/24h and positive Bence Jones proteinuria. The myelogram showed 40% plasma cells, often with a dystrophic appearance.

Serum electrophoresis and immunofixation were performed. Serum agarose gel electrophoresis on Hydrasys 2 Scan Focusing Sebia® revealed the presence of three bands in the gamma region that were distinct and clear. Densitometric analysis of the monoclonal components revealed three monoclonal-looking peaks in the gamma region. A first peak of 9.5 g/L, a second peak at 13.9 g/L and a third peak of 20.1 g/L. And the A/G ratio at 0.29 (Figure 1). Serum protein immunofixation revealed IgA Lambda gammopathy (Figure 2). Free light

chain assay showed kappa free light chains at 843 mg/L, Lambda free light chains at 20070 mg/L and a K/L ratio of 0.04. Thus, a definite diagnosis of multiple myeloma with triclonal peak was retained.
A profile skull X-ray was not performed. And in front of the pelvic symptomatology, a lumbar MRI showed an aspect in favor of secondary spinal and iliac localizations, in particular a tissue mass of the left iliac wing invading the psoas muscle in front and the gluteal muscle in back. Subsequently, whole-body MRI showed multifocal myeloma involvement: cranial, thoracic, spinal, iliac and femoral. All these features were consistent with plasma cell dyscrasia suggestive of multiple myeloma. A serum β2-microglobulin was 11.4 ng/mL. FISH showed absence of delP5 and the rest of the panel was not feasible. The patient died after her first course of chemotherapy.

## III. Discussion

MM is the second most common type of hematologic malignancy after non-Hodgkin's lymphoma. Bone pain, fatigue and recurrent infections are the most common symptoms of MM [4]. MM may pose a diagnostic problem because of the wide variety of symptoms. It should be suspected when bone pain is associated with other systemic symptoms (asthenia, weight loss, etc.) or with abnormalities in the biological tests [5]. Indeed, our case of MM is symptomatic on bone, kidney and erythropoiesis, with a stratification of 3 according to the ISS (International Staging System). Typically, a paraprotein M may appear as a discrete band on agarose gel electrophoresis or as a high, narrow peak or spike in the gamma or beta region or rarely in the alpha-2 region of the electrophoretic pattern. Sera containing a paraprotein M show in 3 to 4% two M proteins (biclonal gammopathy) and rarely three M proteins are found (triclonal gammopathy) [6]. A change of paraprotein can also occur during a relapse of the disease [7].

Janos jakos and al in a review of the literature reported a classification of oligoclonal gammopathies according to the number of secreted paraproteins [8]. The presence of two monoclonal proteins may result from the proliferation of two distinct plasma cell clones, each producing an unrelated monoclonal immunoglobulin, or from the production of two monoclonal proteins by a single plasma cell clone. In addition, the complete class change or switch in a single plasma cell clone results in the production of two M proteins [3].

Immunofixation (IF) is a very sensitive and specific method for determining the type of M protein and is essential for distinguishing a monoclonal peak from a polyclonal increase in immunoglobulins. Immunoelectrophoresis can also be used for the detection of an M protein, but most laboratories do not use it. Immunosubtraction is automated and useful for M-protein immunotyping, has a higher paraprotein detection limit compared to IF [9], and poorly detects non-IgG paraproteins [10].

IgA is the most secreted immunoglobulin and comes after IgG in terms of abundance. They are selectively found in seromucosal secretion, tears, saliva and gastrointestinal secretions. There are two subclasses IgA1 and IgA2 which can be differentiated immunochemically. IgA1 is the major serum subclass (about 80%) and IgA2 is the major subclass in secretions (milk...). A review of the literature revealed the marked predominance of IgA1 MM (93%) over IgA2 MM [11].

Concerning the type of light chains, our patient presented a triclonal peak with IgA lambda type. A French study (n=157) showed that 100 patients (64%) had IgA kappa MM and 57 (36%) had IgA lambda MM [12]. When a monoclonal component is detected by serum protein electrophoresis or immunofixation, further investigations such as bone marrow aspiration or biopsy and radiological examinations are carried out for accurate diagnosis and prognosis [13].

Quantification of Ig and free light and heavy chains is done by nephelometric methods. The determination of serum free light chains (FLCs) has a prognostic role and allows the monitoring of the therapeutic response and the detection of relapses of certain pathologies with monoclonal gammopathy.

The immunoglobulin isotypes also predict the evolution, the non-IgG group is historically associated with the worst prognosis (14). Indeed, our patient belongs to the non-IgG group, she died at an age of 69 years.

A recent study suggests that IgA and light chain MM are associated with poor survival [15]. Early diagnosis and intervention remain essential to prevent irreversible kidney damage in patients with MM, as impaired renal function is one of the prognostic factors along with beta 2-microglobulin concentration, hemoglobin concentrations, hypercalcemia, presence of circulating plasma cells, albumin concentrations, and cytogenetic status [13]. Renal toxicity was found to be variable among the different light chains, suggesting that the structure and concentration of free light chains are determinants [16].

Kyle et al [3] in describing 57 cases of biclonal MM reported that the monoclonal and biclonal nature of the gammopathy showed no difference in prognosis. However, our patient was resistant to treatment, which may suggest that the existence of more than one monoclonal M protein may be a negative prognostic factor that needs to be confirmed in large series.

Some case reports have shown in that triclonal gammopathies were associated with other malignancies and inflammatory pathologies such as multiple myeloma in our patient [17,18]. Triclonal gammopathy has been reported in a patient with plasma cell dyscrasia who subsequently developed AIDS [17]. Non-Hodgkin's

lymphoma has also been associated with triclonal gammopathy [19]. In a review of 24 patients with triclonal gammopathy, 16 were associated with a malignant immunolymphoproliferative disorder, 5 occurred in nonhematologic diseases, and 3 were of undetermined significance [20].

Saito et al (1998) described 2 patients with lymphoma and triclonal gammopathy, and using electron microscopy, they demonstrated that immunoglobulins are synthesized at the same time in a single cell [21].

To assess the risk and prognosis of patients with newly diagnosed MM the revised international scoring system (R-ISS) incorporates a high LDH level, a high beta-2-microglobulin level, a low albumin level, and the presence of high-risk chromosomal abnormalities [22]. In our patient the serum β2-microglobulin was 11.4 mg/L, FISH showed the absence of delP5 and the rest of the panel was not feasible, and prognostic starvation according to R-ISS was not performed.

The high-risk cytogenetic abnormalities are: t(4;14), t(14;16), t(14;20), del(17/17p), gain(1q) and non-hyperdiploidy of the karyotype or del(13) and GEP (Gene expression profiling) which is a high-risk signature [23].

Treatment of myeloma has advanced with the introduction of autologous stem cell transplantation (ASCT) and the introduction of agents such as thalidomide, lenalidomide and bortezomib [7]. Although abnormal protein bands (APBs) on serum electrophoresis are more commonly seen after GACS and considered transient, true triclonal gammopathies are still very rare after treatment [7].

Indeed, the appearance of different bands should be followed with caution as they may represent a true isotype change, in order to predict a possible relapse. In a study by Hall et al [8] it was shown that 48% of patients relapsed 15 months after GACS. GAP after GACS may be oligoclonal or monoclonal in origin. These bands are thought to be due to a transient deregulation of the regenerating B-cell compartment during the post-transplant period. The appearance of APBs can be problematic in the laboratory as they can potentially represent a change in antibody production of the previous plasma cell clone or the emergence of a new malignant clone that is very difficult to discriminate in the first 3-6 months.

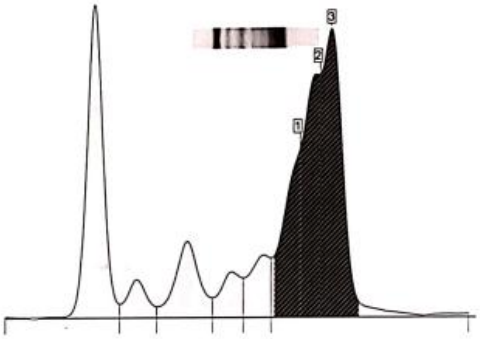
## IV. **Conclusion**

This is the first case of triclonal IgA lambda gammopathy of MM reported in our biochemistry laboratory. Serum protein electrophoresis detected three peaks, in the gamma globulin fraction, whose IgA-Lambda classes were confirmed by immunofixation. However, we could not establish whether the immunoglobulins originated from one cell clone or three unrelated clones. The clinical presentation and response to treatment are similar to other MM cases; nevertheless, these triclonal gammopathies can present significant challenges to the clinical and laboratory staff.

**FIGURES:**

***Eléctrophorèse des protéines sériques***

Sur gel d'agarose HYDRASYS 2 SCAN -SEBIA-




| Fraction | % | | Normales % | Conc g/l | Normales g/l |
|---|---|---|---|---|---|
| Albumine | 22,4 | < | 60,3 - 72,8 | 17,2 | 40,2 - 47,6 |
| Alpha 1 | 3,3 | > | 1,0 - 2,6 | 2,5 | 2,1 - 3,5 |
| Alpha 2 | 8,2 | | 7,2 - 11,8 | 6,3 | 5,1 - 8,5 |
| Beta 1 | 4,2 | < | 5,6 - 9,1 | 3,2 | 3,4 - 5,2 |
| Beta 2 | 5,6 | | 2,2 - 5,7 | 4,3 | 2,3 - 4,7 |
| Gamma | 56,3 | > | 6,2 - 15,4 | 43,4 | 8,0 - 13,5 |

Rapp. A/G : **0,29** P. T. :**77** g/l

| Pic | % | g/l |
|---|---|---|
| 1 | 12,4 | 9,5 |
| 2 | 18,0 | 13,9 |
| 3 | 26,1 | 20,1 |

Figure 1: Serum protein electrophoresis showing 3 peaks

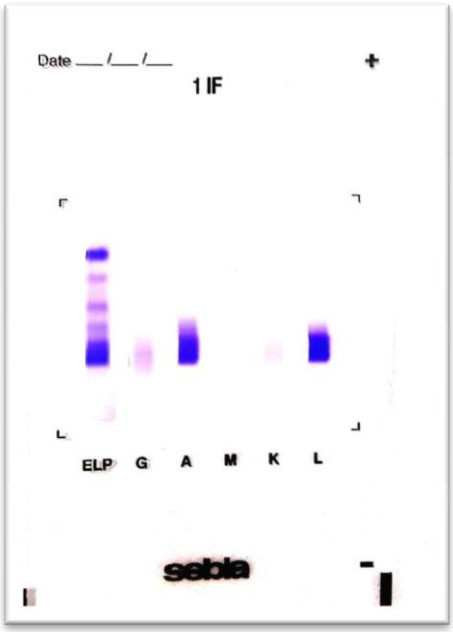



Figure 2: Immunofixation with IgA-Lambda bands

**TABLEAUX :**

| Oligoclonal Gammopathie | Nombre de cas |
|---|---|
| Pentaclonal | 1 |
| Quadriclonal | 3 |
| Triclonal | 10 |
| Biclonal | >300 |

Table 1: Classification of oligoclonal gammopathies in the literature review by Janos jakos et al [10]

**CONFLICT OF INTEREST:**
The authors declare that they have no conflict of interest

**AUTHORS CONTRIBUTION:**
All authors participated in the conception and writing of this manuscript

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