

Oligoclonal gammopathy: An analysis of 253 cases

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Abstract

Background. Oligoclonal gammopathy (OG) is a rare disorder of the lymphoid system that is characterized by the presence of at least 2 distinct monoclonal proteins in a patient's serum or urine. The biological and clinical characteristics of this disease are as yet poorly understood.

Objectives. The study aimed to assess whether there are significant differences between patients with OG regarding the developmental history (i.e., OG diagnosed at the first presentation compared to OG that has developed in patients with an original monoclonal gammopathy) and the number of monoclonal proteins (2 compared to 3). Moreover, we attempted to determine when secondary oligoclonality develops following the original diagnosis of monoclonal gammopathy.

Materials and methods. Patients were analyzed with regard to their age at diagnosis, sex, serum monoclonal proteins, and underlying hematological disorders. Multiple myeloma (MM) patients were additionally evaluated for their Durie–Salmon stage and cytogenetic alterations.

Results. Patients with triclonal gammopathy (TG: $n = 29$) did not differ significantly from patients with biclonal gammopathy (BG: $n = 223$) ($p = 0.81$) in terms of age at diagnosis and the dominant diagnosis (MM was the most common diagnosis (65.0% and 64.7%, respectively)). In both cohorts, myeloma patients were mainly classified to the Durie–Salmon stage III. In the TG cohort, there was a higher proportion of males (69.0%) than among patients with BG (52.5%). Oligoclonality developed at various times after diagnosis (up to 80 months in the investigated cohort). However, the occurrence of new cases was higher during the initial 30-month period following the diagnosis of monoclonal gammopathy.

Conclusions. There are only small differences between patients with primary compared to secondary OG, between BG and TG, and most patients have a combination of IgGκ+IgGλ. Oligoclonality could develop at any time after the diagnosis of monoclonal gammopathy, but it happens more frequently during the first 30 months, with advanced myeloma being the most prevalent underlying disorder.

Key words: immunofixation, multiple myeloma, oligoclonal gammopathy, biclonal gammopathy, triclonal gammopathy

Background

Oligoclonal gammopathy (OG) is a clinical condition characterized by the production of at least 2 separate monoclonal components (M-proteins) detectable in serum or urine. Their presence might be the result of the proliferation of more than 1 clone of pathological plasma cells, or the result of the production of distinct proteins by 1 specific clone.^{1,2} Despite the seemingly low probability of the first alternative, it has already been confirmed by the analyses of mutational profiles that 2 distinct populations of neoplastic plasma cells may exist in an individual patient.^{1,3} Most of the previously published literature concerns biclonal gammopathy (BG). However, the term ‘triclonal gammopathy’ (TG) is also used.^{4,5} Other names, such as ‘biclonal paraproteinemia’ or ‘double gammopathy’ have already been relegated to history.¹ However, pathologists might refer to the manifestation of biclonal gammopathy as ‘double gammopathy manifestation’.²

At least 2 distinct monoclonal proteins can be identified in 1–6% of gammopathies.^{6–8} The specific types of gammopathy include biclonal gammopathy of undetermined significance (BGUS),⁶ together with asymptomatic and symptomatic multiple myeloma (MM). The last one likely develops from a previously diagnosed monoclonal gammopathy of undetermined significance (MGUS)⁴ and other plasma cell dyscrasia, such as light chain amyloidosis. However, the spectrum of hematologic diagnoses identified in patients with OG is not limited to plasma cell dyscrasias. Other underlying abnormalities include lymphoid malignancies (e.g., chronic lymphocytic leukemia, diffuse large B-cell lymphoma or follicular lymphoma) or myeloid malignancies (e.g., acute myeloid leukemia, acute prolymphocytic leukemia or myelodysplastic syndrome).⁶

According to the published data, the clinical picture and response to therapy in patients with biclonal myeloma are similar to those observed in patients with monoclonal myeloma.^{2,9} However, it is still unknown whether the presence of 2nd or further monoclonal proteins affects the incidence or aggressiveness of potential relapse. Based on these results, authors have recommended identical treatment approaches for both groups of patients.⁹

Unfortunately, most of the data on biclonal and triclonal gammopathies come from case reports.^{10–13} Hence, more research is still needed on this subject to determine if there are any specific differences between the conditions.

Objectives

This study aimed to assess the differences between patients in whom OG was recognized during initial diagnosis (further termed as ‘primary OG’) and the remaining patients who had OG diagnosed later (‘secondary OG’).

In secondary OG, we evaluated the time at which the abnormality developed. Then, we evaluated the underlying hematopoietic disorders and possible differences between biclonal and triclonal gammopathies. Moreover, we assessed whether there are differences in the contribution of various monoclonal proteins as indicators of biclonality and triclinality.

Materials and methods

Study design

In this retrospective study, we searched a database of a large, 1000-bed hospital Serum Protein Electrophoresis (SPEP) Laboratory for results containing at least 2 distinct peaks of monoclonal proteins verified with immunofixation (OG). Their presence was the only inclusion criterion in our study. Next, we extracted clinical data from the hospital records of the patients to be included in the study.

Setting

The analysis concerned the results of serum immunofixation of patients who had this test performed during the period from January 2017 to December 2020, and relevant clinical data from all available patient records of those who met the criterion of OG. Data were collected from January 2021 to November 2021.

Participants

We identified 253 patients who met the criterion of OG (137 males and 116 females, 54.2% and 45.8%, respectively) and subsequently analyzed their hospital records. Then, we identified a group of 13 patients with primary OG, that is OG at initial presentation prior to any treatment. The remaining 240 patients had secondary OG, in whom the 2nd peak of monoclonal protein developed later during observation and/or treatment.

Variables

The data available for this study included the patient’s age and sex (available for all patients, $n = 253$), types of monoclonal proteins (2 or more) detectable in the patient’s serum (available for all patients diagnosed during the 4-year period from January 2017 to December 2020 ($n = 253$)), the type of hematopoietic disorder they were diagnosed with (available for $n = 154$ (60.9%)), the date of diagnosis (available for $n = 86$ (34%), the period from 2005 to 2020), Durie–Salmon stage for myeloma patients (available for $n = 69$ (27.3%)), and specific cytogenetic alterations ($n = 16$ (6.3%)).

Data sources

All included data were collected exclusively from the mentioned sources, namely laboratory results and patient hospital records.

Study size

The patients were chosen as participants of the study only based on the results of immunofixation. No other criteria were used for the selection of the participants. The study size of 253 was chosen to maximize the chances of identifying primary OG patients (the smaller portion of the overall cohort) and to minimize the period of observation (4 years).

Quantitative variables

Quantitative variables were analyzed and compared in terms of means, medians and 95% confidence intervals (95% CIs).

Statistical analyses

Comparative analyses were performed using age to segregate the patients. The arranged cohorts were compared with the use of Welch's t-test, with a statistical significance threshold of $p < 0.05$. The normal distribution of the data in the analyzed cohorts was verified using Shapiro–Wilk test, with a threshold of $p < 0.05$ necessary to reject the hypothesis of normality.

Results

Among 253 subjects, 223 patients had 2 distinct M-proteins detectable in serum. In addition, 29 patients had confirmed TG, and 1 patient presented with 4 distinct M-proteins. Cohort sizes and further information are presented in Fig. 1. In the BG patients, the following combinations of M-proteins were the most common: IgG κ +IgG λ ($n = 77$), IgG λ +IgM κ ($n = 21$), IgG κ +IgM λ ($n = 19$), IgG κ +IgM κ ($n = 16$), IgG κ +IgA κ ($n = 14$), IgG λ +IgA κ ($n = 13$), IgG λ +IgA λ ($n = 10$), IgG λ +IgM λ ($n = 8$), IgM κ +IgM λ

($n = 8$), IgG κ +IgA λ ($n = 7$), and IgG κ +IgG λ +IgM κ ($n = 7$), without regard to which M-protein was dominant. The remaining combinations of monoclonal proteins ($n = 53$) were considered miscellaneous to the analysis (the incidence of each combination did not exceed 5 cases). These particular combinations often included less common M-proteins, such as free light chains (κ or λ), free heavy chains (IgG, IgA or IgE), or immunoglobulins (IgE λ or IgD λ).

In TG, the following combinations were found: IgG κ +IgG λ +IgM κ ($n = 7$), IgG κ +IgG λ +IgM λ ($n = 2$), IgG κ +IgG λ +free κ chain ($n = 2$), IgG κ +IgA κ +IgM λ ($n = 2$), IgG λ +IgA κ +free λ chain ($n = 2$), IgG λ +IgA κ +IgA λ ($n = 1$), IgG κ +IgA κ +IgA λ ($n = 1$), IgG κ +IgG λ +IgA κ ($n = 1$), IgG κ +IgG λ +IgA λ ($n = 1$), IgG κ +IgG λ +free κ chain ($n = 1$), IgG κ +IgG λ +free λ chain ($n = 1$), IgG λ +IgA κ +free κ chain ($n = 1$), IgG λ +IgA λ +free λ chain ($n = 1$), IgG κ +IgM κ +free κ chain ($n = 1$), IgG κ +IgM κ +free λ chain ($n = 1$), IgG κ +IgM λ +IgM λ ($n = 1$), IgG κ +IgD λ +free λ chain ($n = 1$), IgG κ +IgM κ +free IgG heavy chain ($n = 1$), and IgG κ +IgM λ +free IgG heavy chain ($n = 1$), without regard to which M-protein was dominant.

Interestingly, free light chains were found in 29 combinations ($n = 18$ with λ and $n = 11$ with κ), 12 of which were found among patients with TG ($n = 29$). The patient with 4 distinct M-proteins also had a detectable free light chain band.

The distribution of M-protein types with their categorization into dominant and secondary M-proteins is shown in Table 1. Analogous results, selectively for TG cases, are shown in Table 2. An individual case of OG with 4 distinct monoclonal proteins displayed the combination of IgG λ +free λ chain+IgG κ +IgM λ .

The patients with primary OG ($n = 13$) were analyzed separately for the types of M-proteins they produced, which were as follows: IgG κ +IgG λ ($n = 3$), IgG κ +IgG κ ($n = 1$), IgG λ +IgA λ ($n = 1$), IgG κ +IgM κ ($n = 1$), IgG κ +IgA heavy chain ($n = 1$), IgG κ +IgA λ ($n = 1$), IgG λ +IgM κ ($n = 1$), IgG λ +IgA κ +free light chain λ ($n = 1$), IgG λ +IgM κ +free light chain λ ($n = 1$), IgG λ +IgA λ +free light chain λ ($n = 1$), and IgG κ +IgA λ +free light chain κ ($n = 1$). The occurrence of IgG κ +IgG λ 3 times among these patients corresponded to the high incidence of this combination of M-proteins in the entire cohort (77 cases, >30% of all combinations) in comparison to other combinations. However, 4 out of 13 patients with primary OG had a specific combination of 2 immunoglobulins + free light chain. There were only 12 such combinations in the entire cohort.

We further investigated whether there is a specific time preference for the development of secondary oligoclonality after the initial diagnosis of monoclonal gammopathy (Fig. 2). As shown, the curve is biphasic, with faster development of biconality during the first 30 months after the diagnosis and a slower rate at later timepoint. However, there is no specific timepoint in which the risk of oligoclonality development is increased compared to other timepoints, or a time when it no longer occurs.

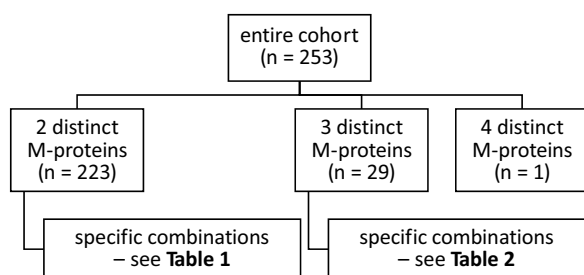


Fig. 1. Sample sizes depending on the number of monoclonal proteins detected with immunofixation

Table 1. Distribution of the most common combinations of monoclonal proteins in the entire cohort (n = 253) regarding dominant and secondary M-proteins

Combination of monoclonal proteins	Incidence
IgGκ+IgGλ	57
IgGλ+IgGκ	20
IgGλ+IgMκ	15
IgMκ+IgGλ	6
IgGκ+IgMλ	14
IgMλ+IgGκ	5
IgGκ+IgMκ	9
IgMκ+IgGκ	7
IgGκ+IgAκ	7
IgAκ+IgGκ	7
IgAκ+IgGλ	7
IgGλ+IgAκ	6
IgGλ+IgAλ	6
IgAλ+IgGλ	4
IgGλ+IgMλ	6
IgMλ+IgGλ	2
IgMκ+IgMλ	8
IgMλ+IgMκ	–
IgAλ+IgGκ	5
IgGκ+IgAλ	2

In each combination, the dominant protein is written first, followed by the secondary protein. Apart from included combinations, there were miscellaneous combinations of M-proteins. These combinations often included free light chains (κ or λ), free heavy chains (IgG, IgA or IgE) and immunoglobulins (IgEλ or IgDλ) as components.

The development of oligoclonality occurred on average after 28.8 months (95% CI: 21.3–36.3 months). Notably, approx. 75% of cases occurred within 30 months, a cutoff point chosen to separate different phases of the Kaplan–Meier curve.

Among the patients with an available diagnosis (n = 154), there were 133 patients with BG, 20 patients with TG and 1 patient with 4 M-proteins. In BG patients, it was possible to distinguish subgroups solely with plasma and lymphoplasma cell dyscrasia (n = 111), and classify these patients based on another accompanying disorder (n = 22). Furthermore, in the subgroup of patients with another disorder, it was possible to distinguish those with lymphoid (n = 11), myeloid (n = 8), other neoplasia (n = 1), and non-neoplastic accompanying diseases (n = 2). However, the subgroup with plasma cell dyscrasia included MM (n = 86 (64.7%)), OG of uncertain significance (n = 11), MM + amyloidosis (n = 7), Waldenström's macroglobulinemia (MWalden) (n = 4), light chain deposition disease (n = 1), amyloid light-chain (AL) amyloidosis (n = 1), and plasmacytic leukemia (n = 1). Interestingly, OG with other lymphoid malignancies included chronic lymphocytic leukemia (CLL) (n = 4), marginal zone lymphoma (MZL)

Table 2. Clinical and laboratory characteristics of the patients with triclonal gammopathy (n = 29)

Patient No.	Monoclonal proteins detected with immunofixation	Diagnosis
1	IgGκ+IgGλ+IgMκ	unknown
2	IgAκ+IgGλ+free λ chain	MM
3	IgGλ+IgMκ+IgGκ	AML
4	IgGλ+IgAλ+IgAκ	unknown
5	IgAκ+IgAλ+IgGκ	unknown
6	IgMλ+IgAκ+IgGκ	CLL
7	IgGκ+IgGλ+IgMλ	MM
8	IgGλ+IgMκ+IgGκ	MM
9	IgGλ+IgGκ+IgMκ	unknown
10	IgMκ+IgGκ+IgGλ	unknown
11	IgMκ+IgGκ+IgGλ	unknown
12	IgMκ+IgGκ+IgGλ	unknown
13	IgG heavy chain+IgMκ+IgGκ	splenic lymphoma
14	IgGλ+free λ chain+IgMκ	MM
15	free λ chain+IgGλ+IgAκ	MM
16	IgGκ+IgAκ+IgMλ	SLL
17	free λ chain+IgGλ+IgAλ	MM
18	IgGκ+IgG heavy chain+IgMλ	MM
19	IgGκ+IgDλ+free λ chain	MM
20	IgMκ+IgMλ+IgGκ	MWalden
21	IgAκ+free κ chain+IgGκ	unknown
22	IgGλ+IgGκ+free κ chain	unknown
23	IgGκ+IgGλ+IgAλ	MDS
24	IgMκ+free κ chain+IgGλ	MM
25	IgAκ+IgGκ+IgGλ	MM
26	IgGκ+free κ chain+IgGλ	MM
27	IgGκ+free κ chain+IgGλ	MM
28	IgGκ+IgGλ+free λ chain	MM
29	IgGκ+IgGλ+IgMλ	glomerulonephritis

MM – multiple myeloma; AML – acute myeloid leukemia; CLL – chronic lymphocytic leukemia; SLL – small lymphocytic lymphoma; MWalden – Waldenström's macroglobulinemia; MDS – myelodysplastic syndrome.

(n = 3), diffuse large B-cell lymphoma (DLBCL) (n = 2), small lymphocytic lymphoma (SLL) (n = 1), and mantle cell lymphoma (MCL) (n = 1). Oligoclonal gammopathy cases with myeloid malignancy included acute myeloid leukemia (AML) (n = 5), myelodysplastic syndrome (MDS) (n = 2) and chronic myeloid leukemia (CML) (n = 1). There was also a case of OG with adenocarcinoma (n = 1). Finally, there were individual cases of OG patients with primary autoimmune thrombocytopenia and autoimmune hemolytic anemia (Fig. 3).

Among 20 patients with TG and available diagnoses, there were 14 cases of plasma cell dyscrasias, including MM (n = 13 (65%)) and MWalden (n = 1). There were also 3 cases of lymphoid neoplasias: CLL (n = 1), SLL (n = 1) and splenic lymphoma (n = 1); 2 cases of myeloid neoplasias: AML (n = 1)

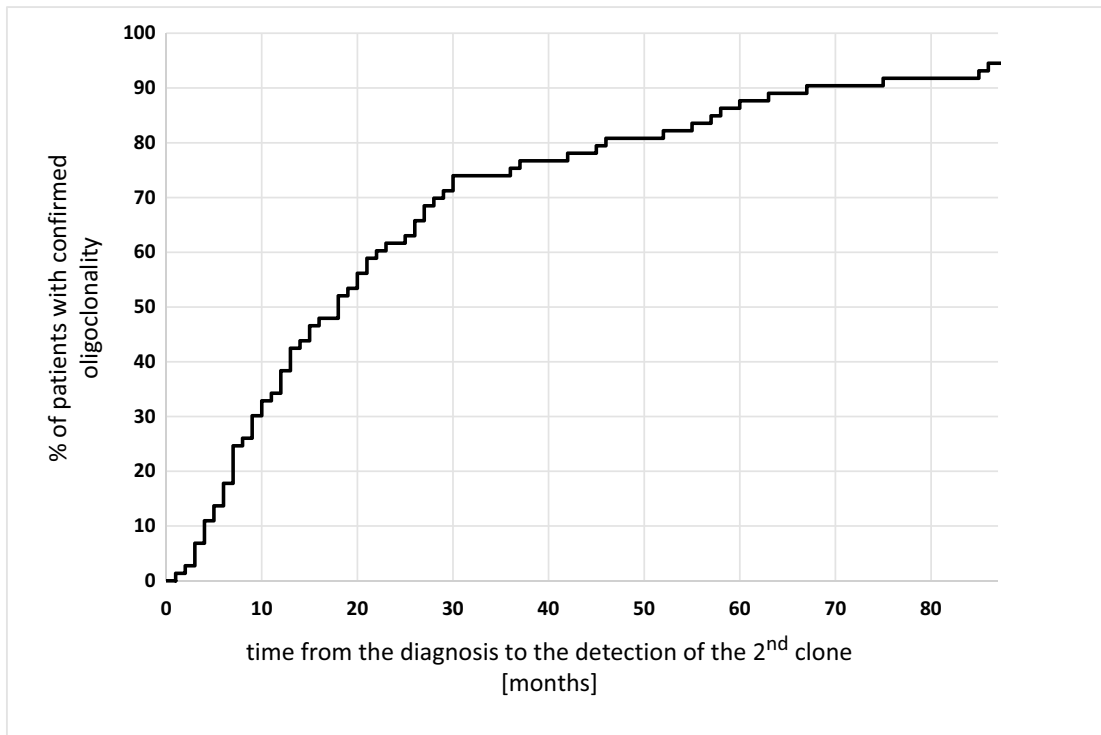


Fig. 2. Kaplan–Meier curve illustrating the amount of time required to detect a 2nd clone using immunofixation in patients with secondary oligoclonal gammopathy (OG) after the diagnosis (n = 73; the date of diagnosis available). Every event is defined as the detection of the 2nd clone in the serum of a single patient (the detection of OG). The figure presents cumulative data, and no data have been censored during this analysis. Therefore, the total number of events for every time interval is 73

time (months)	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80
cumulative number of events	10	24	34	41	46	54	54	56	58	59	61	64	65	66	67	67
total number of events	73	73	73	73	73	73	73	73	73	73	73	73	73	73	73	73

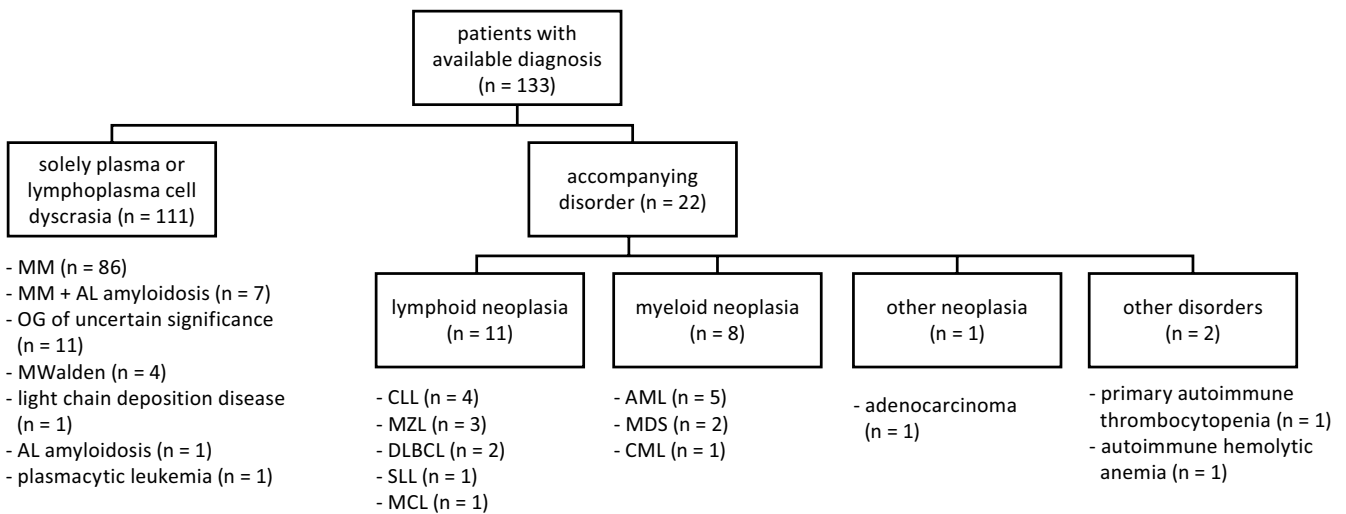


Fig. 3. The spectrum of established diagnoses in patients with biconal gammopathy (BG) (n = 133)

MM – multiple myeloma; AL – amyloid light-chain; OG – oligoclonal gammopathy; MWalden – Waldenström’s macroglobulinemia; CLL – chronic lymphocytic leukemia; MZL – marginal zone lymphoma; DLBCL – diffuse large B-cell lymphoma; SLL – small lymphocytic lymphoma; MCL – mantle cell lymphoma; AML – acute myeloid leukemia; MDS – myelodysplastic syndrome; CML – chronic myeloid leukemia.

and MDS (n = 1); and 1 case of OG resulting from a non-neoplastic disorder, namely glomerulonephritis with vasculitis.

The patient with 4 distinct M-proteins was diagnosed with chronic myelomonocytic leukemia (CMML), a unique diagnosis throughout the entire cohort.

Diagnoses were available for all patients with primary OG (n = 13) and in all cases, plasma cell or lymphoplasma

cell dyscrasia was detected, where the most common was MM (n = 11 (84.6%)). Among them, there was 1 case of MM + amyloidosis and 1 MM + light chain deposition disease. The remaining diagnoses were MWalden and OG of uncertain significance.

Regarding the age at diagnosis (data available for n = 86), the patients with primary OG (n = 12) were significantly

Table 3. Comparison of biclonal and triclonal gammopathies

Compared variables	Biclonal gammopathy	Triclonal gammopathy
Cohort size, n	223	29
Sex (males compared to females)	52.5% compared to 47.5%	69.0% compared to 31.0%
Age at diagnosis [years]	61.6 (95% CI: 59.4–63.8)	63.2 (95% CI: 55.9–70.6)
Most common diagnosis	MM (64.7%)	MM (65.0%)
Durie–Salmon stage (MM)	mainly IIIA and IIIB	mainly IIIA and IIIB
Laboratory findings	<ul style="list-style-type: none"> – IgGκ+IgGλ as the most common combination of monoclonal proteins (>30%) – combinations often include IgG, followed by IgM and IgA – free light chains as distinct proteins occur rarely (17/223) 	<ul style="list-style-type: none"> – high diversity of combinations – all combinations include IgG, often IgM or IgA – free light chains as distinct proteins occur often (12/29)

95% CI – 95% confidence interval; MM – multiple myeloma; Ig – immunoglobulin.

older (mean: 70.8, 95% CI: 66.4–75.3, median: 70.5) than the patients with secondary OG (n = 74) (mean: 60.3, 95% CI: 58.1–62.5, median: 62) (p = 0.0004, Welch's t-test), and the data were normally distributed in both cohorts (p = 0.578 and p = 0.584, respectively, Shapiro–Wilk test). However, no difference in age was observed between patients with TG (n = 26) (mean: 63.2, 95% CI: 55.9–70.6, median: 63.5) and BG (n = 60) (mean: 61.6, 95% CI: 59.4–63.8, median: 63.0) (p = 0.81). A comparative analysis of patients with BG and TG is shown in Table 3.

Notably, 11 out of 13 patients (84.6%) with primary OG were males, while in patients with secondary OG (n = 240), the occurrence of both sexes was similar (126 males and 114 females, 52.5% and 47.5%, respectively). Interestingly, in the TG cohort, there were 20 males (69.0%) and 9 females (31.0%). The patient with 4 detectable monoclonal proteins was also male.

The analysis of Durie–Salmon stages in OG myeloma patients (data available for n = 69 (27.3%)) revealed the following results: IA – n = 6, I – n = 1, IB – n = 0, IIA – n = 12, II – n = 2, IIB – n = 3, IIIA – n = 25, III – n = 0, IIIB – n = 20. Therefore, the majority of patients developed oligoclonality in the advanced stages of myeloma, sometimes years after the primary diagnosis of monoclonal gammopathy. Conversely, in patients with primary OG (data available for n = 6), 2 patients were classified to stage IA, 2 patients to IIA, 1 to IIIA, and 1 to IIIB. For myeloma patients with 3 detectable clones, Durie–Salmon staging was available for 8 out of 13 cases. The results were as follows: 1 patient with IA, 1 patient with IIA, 3 patients with IIIA, and 3 patients with IIIB stage. While no statistical comparison was possible with these numbers, the data did not reveal major differences between the BG and TG cohorts.

The cytogenetic analysis was only performed in 16 out of 253 patients but revealed 10 individuals with karyotype abnormalities, as follows: t(4,14) in 2 patients and del(17) + del(1), IGH/FGFR3 fusion with rearrangements of IGH, t(11,14), hyperdiploid, del(17p–), deletion of TP53, monosomy of 17p, and partial monosomy of 17p + partial deletion of TP53, each in 1 patient. Among patients with

primary OG, cytogenetic alterations were not found. Finally, the patient with monosomy of chromosome 17p had 3 detectable M-proteins in serum.

Discussion

This study analyzed the problem of secondary OG and provided a comparison of BG and TG for the first time. We observed that the development of both biclonality and triclinality is frequently a late event in the evolution of MGUS, often observed when MGUS progresses to MM. Furthermore, most cases of so-called primary OG had symptomatic MM. It suggests that they underwent an evolution from monoclonal gammopathy during undiagnosed disease and not as a primary event. Furthermore, our data suggest that the spectrum of both biclonality and triclinality is very large and every theoretically possible combination of M-proteins may be observed.

We failed to associate any specific event in a disease course (transformation, treatment, progression, remission, stabilization) with the development of oligoclonality (the detection of the 2nd or subsequent clone). Therefore, we performed a time analysis with the Kaplan–Meier curve (Fig. 2). Some studies postulate potential emerging factors of OG, such as autologous hematopoietic stem cell transplantation.⁶ However, there are no prospective cohort studies that have analyzed this aspect of the disease. Therefore, the etiology of OG remains unknown and no contributing factors have been identified.

There are 2 major possible mechanisms for developing oligoclonality. One possibility is that 2 or more clonally different plasma cell dyscrasias co-occur in the same patient. The other is that BG and TG represent an evolution of the primary clone with subclones derived from cells that underwent additional mutational events. Recent analysis with next-generation sequencing has revealed that aberrations in the TP53 signaling pathway are responsible for the occurrence of multiple, synchronous primary cancers.¹⁴ Moreover, and specifically for OG, the cases of 2 (or more)

monoclonal immunoglobulins that contain distinct light chains (κ and λ) might be considered truly biclonal, since no molecular mechanism of changing light chain expression has been described so far.¹⁵ Such a statement has already been made by some authors³ and our study reveals numerous cases of oligoclonal gammopathies where M-proteins include immunoglobulins with different light chains. This phenomenon seems to occur too frequently to be just a coincidence without any underlying mutational background. Lastly, polymerase chain reaction (PCR) and immunofluorescence (IF) analyses of clonal relationship in patients with BG imply that 2 independent clones can coexist synchronously in individual patients, even when the clones produce immunoglobulins with the same type of light chain (κ and λ).¹⁶

We failed to identify major differences between primary and secondary OG, except for primary OG patients of more advanced age. The similarities between both groups (primary compared to secondary OG) have been observed regarding the dominant diagnosis. In both groups, MM or MM + comorbidities were the dominant diagnoses, which remains consistent with earlier findings.⁴ We have also failed to identify significant differences between patients with biclonal compared to triclonal gammopathies when comparing age, underlying disorder and the dominant combinations of monoclonal proteins that are present. In the only other analysis of TG concerning 6 cases, there were 2 cases of MWalden, 1 case of non-Hodgkin lymphoma, 1 case of polycythemia vera, and 2 cases without any hematopoietic disease.¹⁷ However, the same analysis revealed that 64.6% of TGs were detected in lymphoproliferative diseases, based on all known cases.¹⁷ The IgG occurred the most often in combinations of monoclonal proteins in all groups. This is not surprising, since this serum protein is also detectable in the majority of monoclonal gammopathy cases (followed by IgM and IgA).^{4,18} The additional 3rd M-protein in patient serum was often a free light chain. Furthermore, free light chains tended to be detectable as a part of a triclonal combination (12/29), as opposed to biclonal combinations (17/223). The reasons for the presence of additional free light chains in patients with TG (especially the patients with primary OG) remain unknown, and this phenomenon requires further research and clarification.

Other publications concerning TG are limited to case reports, for example, IgM κ +IgG κ +IgA κ ,^{4,19} IgG κ +IgG λ +IgA λ ,⁵ IgG κ +IgG λ +IgM λ ,²⁰ or IgA κ +IgG κ +IgM κ .²¹ The case of IgA κ + free κ light chain + free λ light chain has also been reported.²² However, our analysis shows that 29/253 (11.4%) cases represent TG, suggesting that the magnitude of the phenomenon is larger than expected.

While data concerning cytogenetic alterations are limited (10 out of 16 tested patients), they only identified changes that have already been found in MM cases.²³ However, they appear to be quite common in OG cases.

Limitations


The main limitation of the study was the availability of clinical data, such as diagnoses. The lack of data resulted from the fact that OG is a rare disorder. Moreover, we did not identify any comprehensive disease mechanism underlying OG.


Conclusions


The diagnosis of patients with primary OG is more often established in males in older age (approx. 10 years older) than in patients with secondary OG. The detection of secondary OG often (in approx. 75% of cases) occurs up to 30 months after the initial diagnosis. Moreover, there are laboratory and clinical findings that are specific to patients with primary OG and TG cases. Despite the findings of this study, OG remains a poorly understood disorder and more research, especially prospective studies, is necessary to support these conclusions. It will take more time for the detailed pathogenesis of the disease to be established.

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