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THE ASSOCIATION OF TOTAL PARAPROTEIN, TOTAL PROTEIN, ALBUMIN AND GLOBULIN CONCENTRATION WITH PARALLEL BANDS PRESENCE IN IMMUNOFIXATION ELECTROPHORESIS: A SEVEN-YEAR RETROSPECTIVE STUDY

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ABSTRACT

The presence of parallel bands at all heavy and light chain lanes of immunofixation electrophoresis (IFE) gel obscures paraprotein isotyping, thus preventing accurate diagnosis of paraproteinemia. Several reasons, including immunoglobulin polymerization and rheumatoid factor presence, have been implicated as the possible causes. The high concentration of several routine biochemistry parameters is believed to be a contributory factor too, but the association is yet to be determined. This study aims to determine the association of total protein, albumin, globulin, and total paraprotein concentrations with samples showing parallel bands at all lanes of IFE. Serum protein electrophoresis (SPEP) and IFE samples sent from May 2015 to May 2022 were screened and grouped into plasma cell myeloma (PCM) and non-PCM cases. The total protein, albumin, globulin, and total paraprotein were compared with the presence of parallel bands in PCM and non-PCM cases. From 1150 samples, 45 (3.9%) exhibited parallel bands at all lanes. 34 (75.6%) belong to PCM samples. Total paraprotein concentration among samples with parallel bands at all lanes demonstrated a significant difference with median (IQR) of 7.6 (20.4) g/L in PCM, and 2.0(4.4) g/L in non-PCM (p=0.039). However, no statistical difference was observed in total protein, albumin, and globulin concentration for both groups (p=0.354, p=0.948, p=0.506, respectively). Only total paraprotein concentration could influence the presence of parallel bands at all lanes of IFE. Further studies using a larger sample population could elicit this finding better and help determine a specific total paraprotein cut-off associated with parallel bands at all lanes.

1.0 INTRODUCTION

A paraprotein is a monoclonal immunoglobulin or light chain present in the blood or urine produced by a clonal proliferation of mature B cells, most commonly plasma cells. The presence of paraprotein is almost always associated with plasma cell neoplasm (PCM). In individuals aged >50 years, the incidence of a paraprotein is 3.2% [1]. International Myeloma Working Group (IMWG) described the presence of paraprotein with quantitation of <30 g/dL as monoclonal gammopathy of undetermined significance (MGUS), while that of with paraprotein concentration of >30 g/dL as smouldering myeloma [2]. Besides, quantitation of paraprotein is also useful for monitoring of disease process when plasma cells are >10% in the bone marrow [2]. Serum protein electrophoresis (SPEP) is a facile and cheap method used to separate different types of proteins: alpha-1, alpha-2, beta, and gamma, based on their net charges, sizes, and shapes. The protein was detected after the separation process by staining them with an amido black stain. The quantitative measurement of the proteins was made using densitometers, where measurement of the light absorbance on the electrophoretic pattern was made, resulting in a proportionate concentration of protein

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with each peak. The appearance of monoclonal bands on serum protein electrophoresis prompts an immunofixation electrophoresis (IFE) for confirmation of the specific paraprotein heavy and light chain isotype. Although IFE remains a key method for paraprotein isotyping, it is not free from interference; the presence of parallel bands across all heavy and light chain lanes often obscures accurate isotype identification, necessitating repeated analysis and complicating the reporting process [1-5]. The cause of such a phenomenon possibly resulted from immunoglobulin anti-immunoglobulin (Ig-anti-Ig) complex formation or nonspecific cryoglobulin aggregates [4, 6]. Although PCM is almost always associated with a single clone, rarely, it can also be represented by biclonal or triclonal paraproteins [4]. However, immunoglobulin polymerization and cryoglobulins are even more common than true biclonal gammopathy [3]. This is usually the case in IgA and IgM paraproteinemia [7-8]. Liu et al. (2019) reported a case of Waldenström macroglobulinemia with persistent bands at all IFE lanes, which did not resolve following the usual formulation of reducing agents [6]. Meanwhile, paraproteins could also exhibit rheumatoid factor (RF) activity, forming parallel bands that could be either a benign occurrence or a true underlying triclonal gammopathy [4].

Additionally, artefactual bands at all lanes could also be attributed to pre-analytical influences such as erroneous formulation of acidic reagents in urine samples and a carryover effect, often apparent at the applicator points, sometimes with equal intensity [9]. The causes to this parallel band phenomenon might be an indicator of a high total protein concentration. Although the mechanism of high total protein causing the parallel band was yet to be established, the parallel band has thus far caused a diagnostic challenge to SPEP interpretation and a delayed result reporting as the presence of parallel bands requires further pretreatment steps with beta-mercaptoethanol (BME) in order expose a distinct paraprotein band following dissolution of the other interfering parallel bands [3]. Here, we intend to see the association of total protein, albumin, globulin, and total paraprotein concentrations with parallel bands at all lanes in IFE serum samples.

2.0 METHODS AND MATERIALS

The study is retrospective and conducted with ethical approval from the institutional research committee. All data were obtained from a single tertiary health centre located in an urban area of a city from May until December 2022. Sample sizes were estimated using a prevalence formula based on retrograde plasma cell myeloma incidence obtained from the laboratory archives from 2015 to 2022. The prevalence of paraproteinemia derived from the laboratory archives ranged from 9.9% to 21%, with an average of 14.6% per year. Considering the prevalence of 14.6% and 30% dropout from the exclusion criteria, the minimum sample size (n) required was 60. All SPEP and IFE samples sent from May 2015 to May 2022 were screened. 1270 samples were extracted, and 1150 were selected according to the inclusion and exclusion criteria. Inclusion criteria include all serum protein electrophoresis and immunofixation examination samples sent from May 2015 to May 2022. Exclusion criteria include external quality assurance (EQA) samples, missing immunofixation examination test gel, and samples with atypical bands (i.e., dimeric, multiple clones). Each sample's total paraprotein, serum protein, albumin, and globulin levels were extracted from the integrated laboratory information management system (ILMS). The patient demographic data and the final diagnosis were extracted from the patient's electronic records in Figure 1. The parallel bands were retrospectively retrieved from the gel electrophoresis and immunofixation test performed. All the sera sample included were analysed using the laboratory's current system, comprising a thin-layer agarose gel (HYDRAGEL 30 Protein (E), Sebia, Lisses, France) and the semi-automated Hydrasys 2 analyser, with electrophoresis performed according to the manufacturer's instructions. Following electrophoresis, the gels were dried, stained with amido black, de-stained, and scanned using the Sebia GELSCAN densitometer to generate electrophoretogram fractions based on band intensity. The area under the curve for each fraction was used to calculate its concentration (g/L), relative to the total area corresponding to the serum total protein concentration, quantified using the perpendicular drop method.

The serum total protein was determined based on the Biuret principle on the Abbott Alinity c system. To minimise bias, two Chemical Pathologists independently reviewed the stained gels and electrophoretograms, verifying the correct positioning of delimiters and confirming the presence of paraprotein with and without parallel bands. Further investigation steps for samples with parallel bands were also confirmed from sequential treatment with Fluidil or reducing agent. Samples showing parallel bands but confirmed by IF to be oligoclonal patterns, biclonal or triclonal were excluded from the study. All the samples were identified and grouped into PCM and non-PCM cases. PCM samples were confirmed with the patient's discharge summary report and bone marrow aspiration and trephine biopsy (BMAT) findings

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based on the recommendation by the 2014 IMWG guidelines [2]. PCM samples include those with MGUS, smouldering multiple myeloma (SMM), light chain multiple myeloma (LCMM), and multiple myeloma (MM). Non-PCM samples did not fulfil the criteria for MGUS, SMM, LCMM, or MM based on the patient's records and laboratory archives or those without the BMAT result. All data were tabulated in Microsoft Excel before analysis using the statistical software were made. Figure 1 shows the data collection process in this study.

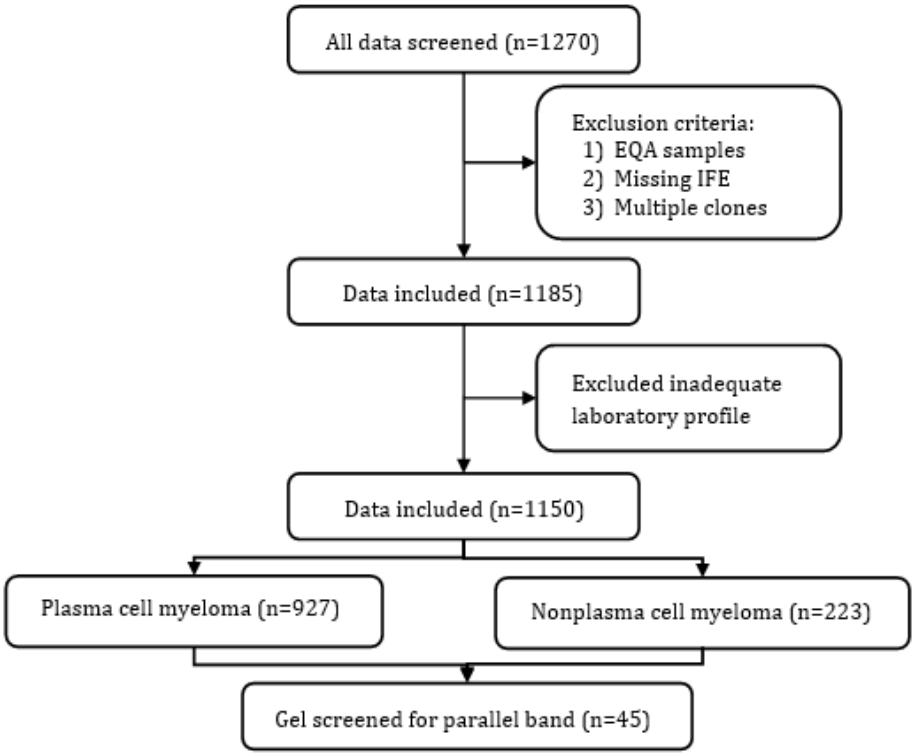

Figure 1. Data collection workflow process

*Abbreviations: EQA = External quality assurance, IFE = Immunofixation Electrophoresis

Data was analysed using SPSS version 28 software. The data distribution for cases with parallel bands was determined using the Kolmogorov-Smirnov test, showing a non-normal distribution ($p<0.05$). According to Spronk et al. (2019), the prevalence was calculated as a one-year prevalence using the number of parallel band cases per year as the numerator and the number of paraproteinaemia cases detected per year (as the denominator) [10]. All continuous data were represented in mean and standard deviation, while non-continuous data were presented as median and interquartile range. The differences in total protein, albumin, globulin, and total paraprotein between the presence of a parallel band in PCM and non-PCM cases were determined using the Mann-Whitney U test. The result's significance is considered when the p-value is less than 0.05.

3.0 RESULTS

One thousand one hundred fifty samples were analysed after the inclusion, and exclusion criteria were applied. Nine hundred twenty-seven samples belong to PCM cases, while 223 belong to non-PCM cases. The mean age for those with PCM and non-PCM samples was 64.5 and 64.6, respectively as in Table 1. For PCM samples, 457 (49.3%) were men, and 470 (50.7%) were women. The non-PCM samples were contributed by 133 (59.6%) men and 90 (40.4%) women. The total serum protein, albumin, globulin, and paraprotein concentrations were generally higher in non-PCM samples. The total serum protein for each PCM and non-PCM sample was 73.0 g/L and 74.5 g/L, respectively. The albumin concentration was 34.4 and 40.0 g/L for each PCM and non-PCM sample. The globulin concentration was 38.6g/L for PCM and 43.6 in non-PCM. The biggest proportion of clones among both PCM and non-PCM samples was observed as IgG kappa in origin, followed by IgG lambda. Other paraprotein comprises of IgM kappa and lambda, IgA kappa and lambda, and lambda and kappa light chain. A single case of IgD lambda was observed in the PCM sample, but none was found in the non-PCM sample as in Table 1.

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Table 1. Demographic and biochemical profile of the study population

		PCM (n=927)	Non-PCM (n=223)
Age (years)[a], mean±SD		64.5 ± 9.4	64.6 ± 13.0
Sex[b], n (%)	Man	457 (49.3)	133 (59.6)
	Woman	470 (50.7)	90 (40.4)
Total protein[a] (g/L)		73.0 ± 16.8	74.5 ± 15.7
Albumin[a] (g/L)		34.4 ± 6.1	40.0 ± 8.2
Globulin[a] (g/L)		38.6 ± 18.7	43.6 ± 16.9
Paraprotein concentration[a] (g/L)		12.1 ± 17.1	12.5 ± 16.1
The presence of parallel band[b]	Yes	34 (3.7)	11 (4.9)
	No	893 (96.3)	212 (95.1)
Paraprotein[b]	IgGK	498 (53.7)	88 (39.5)
	IgGL	178 (19.2)	46 (20.6)
	IgAK	111 (12.0)	6 (2.7)
	IgAL	66 (7.1)	22 (9.9)
	IgMK	1 (0.1)	25 (11.2)
	IgML	8 (0.9)	13 (5.8)
	KLC	10 (1.1)	8 (3.6)
	LLC	54 (5.8)	15 (6.7)
	IgDL	1 (0.1)	0(0)

*Abbreviations: Ig = Immunoglobulin, K = kappa light chain, L = Lambda light chain, LC = light chain,
[a]mean ± standard deviation, [b]n (%)

Of all samples with positive paraprotein, 45 (3.9%) appeared to have parallel bands at all heavy and light chain regions, with 34 (75.6%) belonging to PCM samples. IgG kappa showed the highest proportion, n (%) of parallel bands, 17 (20.0%), followed by IgG lambda, 10 (29.4%), and IgA kappa, 4 (11.8%). IgA lambda, IgM lambda, and lambda light chain were shown by only 1 (2.9%) case each. Mann-Whitney test is used to compare several biochemical parameters with the presence of parallel bands in PCM and non-PCM cases. Table 2 shows the total protein for PCM and non-PCM cases show median (IQR) concentration of 70.0 (16.8) g/L and 62.0 (19.0) g/L respectively. However, the median of the total serum protein concentration in both PCM and non-PCM groups is not statistically different (p=0.354). Similarly, there is also no statistical difference observed in albumin (p=0.948), and globulin (p=0.506) concentration for both groups (p=0.948 and p=0.506 respectively). The total paraprotein concentration has a median (IQR) of 7.6 (20.4) g/L in PCM, while in non-PCM, the concentration was only 2.0 (4.4) g/L, resulting in a statistically significant difference between the two groups (p=0.039).

Table 2. Differences in laboratory profiles for cases with the presence of parallel bands at all lanes

	Parallel band (n=45)		*U, p*-value
	PCM (n=34)	non-PCM (n=11)	
Total Protein[a] (g/L)	70.0 (16.8)	62.0 (19.0)	*U*=151.5, *p*=0.354
Albumin[a] (g/L)	32.5 (10.3)	34.0 (17.0)	*U*=184.0, *p*=0.948
Globulin[a] (g/L)	33.5 (24.3)	31.0 (11.0)	*U*=161.0, *p*=0.506
Paraprotein concentration[a] (g/L)	7.6 (20.4)	2.0 (4.4)	*U*=109.0, *p*= 0.039*

[a]median (IQR), *The mann-whitney U test is reported in *U*, *p*-value where $p < 0.05$ is considered significant

4.0 DISCUSSION

Our study reveals that samples with parallel bands at all lanes of IFE are more commonly observed in PCM compared to the non-PCM samples. IgG kappa and IgG lambda were mostly associated with parallel bands, followed by IgA kappa. We observed only 1 parallel band in IgM lambda and none in IgM kappa cases. Contradictorily, literature described the occurrence of parallel bands at all lanes of IFE as more commonly associated with IgA and IgM paraprotein due to their tendency for polymerization [7-8]. Whereas IgG in combination with IgA is more commonly associated with biclonal gammopathy [11]. Only the total paraprotein concentration between PCM and non-PCM cases shows a statistically significant difference ($p<0.05$). In some circumstances, paraprotein tends to exhibit RF activities, especially when bands appear parallelly at both heavy and light chain lanes [6]. In cases involving IgM paraproteins, a biclonal or triclonal pattern on IFE warrants rheumatoid factor titre measurement [4]. This owes to the rarity of both true biclonal and triclonal gammopathy. A multicentre study in the UK reveals only a 0.91% prevalence of biclonal gammopathy [12]. They usually exhibit parallel bands at two different light chains rather than 2

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different heavy chains [13]. A study in Poland reveals a proportion of only 11.4% for triclonal gammopathy [14]. Cryoglobulin formation is also another cause of the appearance of monoclonal bands at all lanes [4]. Positive cryoglobulin samples have been associated with detectable paraproteins and rheumatoid factor activity with 97% to 98% sensitivity [15]. However. whether or not these factors contributed to the statistically significant results in our study mandates additional investigations, such as rheumatoid factor measurement. Suppressed albumin and raised globulin levels could be observed in patients with paraproteinemia [16-18].

In our study, we intended to see the statistically significant difference of these biochemical markers between both PCM and non-PCM cases presented with parallel bands. However, there is no significant difference observed, perhaps owing to the single-centred and limited sample availability. Dissolution of cryoglobulins can be facilitated by adding a diluent, such as Fluidil, to the sample prior to analysis on the IF gel. However, a reducing agent is often required to pre-treat the sample [6]. BME is commonly used to resolve cryoglobulins and immunoglobulin polymerisation, although stronger reducing agents such as sodium dodecyl sulfate (SDS) and dithiothreitol (DTT) have also been employed [3, 5-6]. These agents act by breaking disulfide bonds, thereby helping to dissociate cryoglobulins and immunoglobulin aggregates. Liu et al. (2019) employed different formulations of BME with the addition of SDS before isotyping could be properly made [6]. Incubation at different temperatures has also been attempted, despite no obvious changes being observed at both 37 °C and room temperature [6]. Othman 2006 demonstrates no resolution of bands at 10 minutes and 30 minutes of pre-treatment with 10% BME, but the bands resolve after 60 minutes of the pre-treatment process [5]. In our study, not all samples with parallel bands were subjected to the use of reducing agent, especially those with clear-cut diagnosis when correlated with BMAT findings, and some parallel bands resolved following fluidal without the need of reducing agent. Measurement of rheumatoid factors could help to distinguish true bands with aggregates of the immune complex due to rheumatoid activity [4]. A negative RF rules out RF interference and vice versa [4]. However, the positivity of RF could not conclude the isotype of a paraprotein, therefore, re-analysis might require pre-treatment precipitation with heavy chain antiserum [4]. As a cost-saving measure, we believe that the resolution of parallel bands using reducing agents and additional incubation steps is not mandatory for all SPEP with paraprotein bands with parallel bands on IFE. To implement a targeted approach, this could be initiated at a specific total paraprotein concentration cut-off.

Nevertheless, the specific paraprotein cut-off associated with parallel bands must first be determined. Resolution of concurrent parallel bands could help prevent confusion during reporting and allow correct isotyping of a paraprotein. This is also particularly crucial for an accurate clinical diagnosis, which determines patient management [3]. Figure 2 below depict examples of IFE without parallel bands and a comparative IFE with faint bands present at all lanes of heavy and light chains. This hinders accurate paraprotein isotyping.

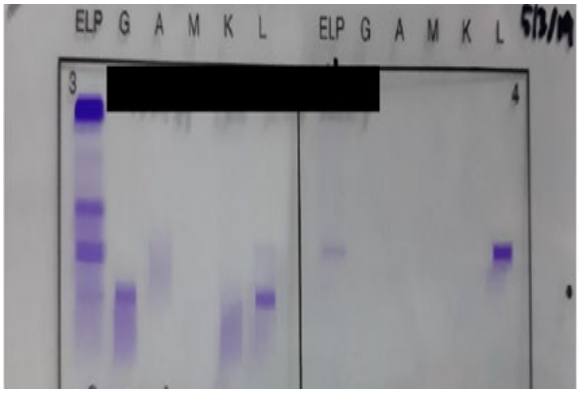

Figure 2. Examples of two serum immunofixation electrophoresis (IFE) routinely done in Chemical Pathology laboratory, HCTM

The accurate isotyping can be made in both samples above. The presence of clear-cut IgG Lambda and Lambda light chain in both samples above permits straightforward reporting of serum electrophoresis (SPEP) results. Literature also described total protein and globulin concentration cut-off as a recognized marker that distinguishes between paraproteinemia and non-paraproteinemia cases [16, 18]. However, this was not demonstrated in our study. We believed further studies using a larger sample size could be done to establish this cut-off reliably. Figure 3 shows the serum sample here exhibits distinct bands over

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the IgG and Lambda lanes. But there are concurrent parallel bands presence at all lanes. This is a single-centred cross-sectional study. Our study lacks distinctive categorization between parallel bands' presence in samples received for diagnosis and those received for monitoring purposes. This study also involves a small sample size. Therefore, validation in future studies with a larger sample size would be beneficial.

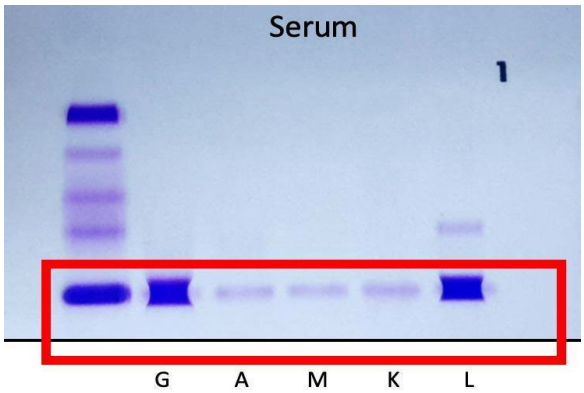

Figure 3: Example of IFE gel with presence of parallel band

5.0 CONCLUSION

Total paraprotein could influence the presence of parallel bands in all lanes of immunofixation electrophoresis. Future studies could investigate the specific cut-off of paraprotein associated with the presence of parallel bands at all lanes of IFE to allow a targeted sample pretreatment process, thus reducing workload and cost.

6.0 CONFLICT OF INTEREST

The authors declare no conflicts of interest.

7.0 AUTHOR'S CONTRIBUTION

Badaruddin, I. A. (Literature review, clinical data collection, and writing of original draft)
Mansor, M. M. (Literature review, clinical data collection, critical revision, and supervision)
Wan Ahmad Fakuradzi, W. F. S. (Statistical analysis)
Ab Rahim, S. N. (Literature review, writing, and formatting)

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