Bisalbuminemia: A rare incidental finding in monoclonal gammopathy

Dr Sanjay Bagade[1], Dr Arshiya Anjum[2]

[1]*Head of the Department of Biochemistry, Basavatarakam Indo-American Cancer Hospital and Research Institute, Hyderabad, India*
[2]*Consultant, department of Biochemistry, Basavatarakam Indo-American Cancer Hospital and Research Institute, Hyderabad, India*

Article Info

Author of correspondence:
Dr Arshiya Anjum, MBBS, MD, Consultant Biochemist, Department of Biochemistry;
E-mail: dr1arshiya@gmail.com; hodbiochemistry@induscancer.com;
Tel.: +91-9704767553; +91-9885574091;
Address:
Basavatarakam Indo-American Cancer Hospital and Research Institute, Road number 10, Banjara Hills, Hyderabad, 500034.

Keywords

Bisalbuminemia, Serum Protein electrophoresis, Capillary electrophoresis, multiple myeloma, rare.

Abstract

Bisalbuminemia is a rare, benign, protein anomaly presenting with two distinct peaks of albumin on serum protein electrophoresis. It reflects the presence of a normal albumin and a modified albumin in the same individual. This condition can be either hereditary or acquired. Bisalbuminemias are more frequently encountered when serum protein electrophoresis is performed with capillary technique, because this offers better resolution compared to the conventional gel electrophoresis. There are very few case reports available in the literature, showing the presence of a bifid albumin peak along with a distinct paraprotein peak in the globulin region in serum protein electrophoresis. Here we are reporting two cases, a 46-year-old male and a 48 year-old male, diagnosed with multiple myeloma, revealing the presence of an extra peak in the albumin region along with a distinct paraprotein band, when the electrophoresis was performed using capillary mode. From these case reports, we wish to reveal the extremely rare nature of this entity and also to acquaint the clinicians and laboratory personnel with this pattern of electrophoretogram.

INTRODUCTION

Albumin is the major constituent of human plasma produced in the liver and has a variety of physiological functions. Besides being essential, it constitutes 60 to 65% of total plasma proteins. Its major function is to maintain oncotic pressure along with the transportation of several endogenous and exogenous molecules. Its antioxidant function protects the body from several oxidizing agents (1). Serum protein electrophoresis (SPE) is an investigation performed routinely for the screening of monoclonal gammopathies. It can be performed using various techniques, with capillary electrophoresis being the most sensitive among them, giving more discrete bands. Electrophoresis pattern normally reveals albumin, the largest peak followed by the next five components of globulins labelled as alpha1, alpha2, beta1, beta2, and gamma. The subsets of these proteins and their relative quantity are the primary focus of the interpretation of serum protein electrophoresis (2). Albumin is usually a tall, single, discrete peak on electrophoretogram. Very rarely, we come across samples giving two peaks in the albumin region, which could be completely distinct peaks or partial splitting of the albumin peak. Structurally, the primary sequence of

albumin contains three major regions with three peptide loops each, suggesting that it arose from gene duplication of some ancestral gene in a tandem rearrangement. Variants of albumin differ from the most common allotype, albumin A, by single amino acid substitutions. It is the presence of these variants which gives splitting of the albumin peak. These variants can be rapid or slow migrating compared with albumin A (3). This phenomenon was first described in the year 1955 by Scheurlen in a diabetic German patient. The incidence of these variants is around 1:1000 to 1:3000. The incidence is reported to be high (1:100) in several tribes of North American Indians (1). This condition can be inherited or acquired. Hereditary bisalbuminemia is a relatively rare genetic disorder, usually revealed by chance. The causative genetic lesion is a point mutation of human serum albumin gene, inherited in an autosomal codominant pattern. At least 77 different mutations in albumin are recognized, 65 of which lead to bisalbuminemia (3). The presence of acquired bisalbuminemia have been described in various pathological conditions like diabetes mellitus, Waldenstrom's macroglobulinemia, multiple myeloma, sarcoidosis, Alzheimer's disease, pancreatic pseudocyst, nephrotic syndrome, chronic kidney disease, and also in patients receiving high doses of penicillin (4). Hereditary type is permanent but the acquired form may be transient. Most of the isoforms of albumin have normal function, and most individuals with bisalbuminemia have normal serum concentrations of albumin. Clinically, no pathological consequences have been reported for bisalbuminemia (alloalbuminemia) and it is being of interest only for human genetics due to its rare incidence. In this study, we present two cases of incidentally detected bifid albumin peaks in newly diagnosed patients of multiple myeloma. Out of the 3360 samples run for serum protein electrophoresis (SPE), during the last five years in our hospital, there were only two patients with a bifid albumin peak showcasing the rarity of the scenario.

CASE REPORTS:

Case 1:

A 46 year old male patient presented with complaints of body pains and aches in multiple joints, for which he was evaluated at an outside hospital, where his investigations were unremarkable, except for the presence of severe anaemia and a high total protein. Anaemia was treated with blood transfusion followed by oral supplements. However, the patient had similar complaints of anaemia and polyarthralgia few months later. In view of recurrent anaemia, high total protein, and persistent polyarthralgia, he was sent to our hospital for further management. In our hospital, the results of serum creatinine, calcium and liver function tests were normal, except for high total protein. Serum protein electrophoresis (SPE) and serum free light chain assay were first performed as screening tests to rule out multiple myeloma. The electrophoretogram of the patient was showing a distinct monoclonal (M) band of 23 g/L in the gamma region along with the presence of a small extra peak in the albumin region and serum free light chain assay was suggestive of kappa type of monoclonal gammopathy. Bone marrow aspiration and biopsy followed by flow cytometry were further done, which confirmed the presence of multiple myeloma. For the management of the disease, the patient was given four cycles of chemotherapy with Lenalidomide, Bortezomib, and Dexamethasone (RVD) regimen. During the course of chemotherapy, SPE was repeated to check for the disease progression every 4 months. All of his electrophoretograms had the presence of the same bifid albumin peak which as depicted in the figures 1 and 2. Now the patient is on maintenance therapy with Bortezomib drug.

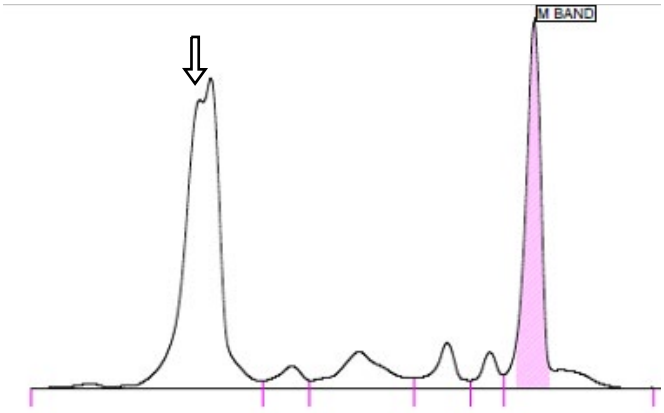

Figure 1: Electrophoretogram of Case-1 at the time of presentation showing bifid albumin along with M band.

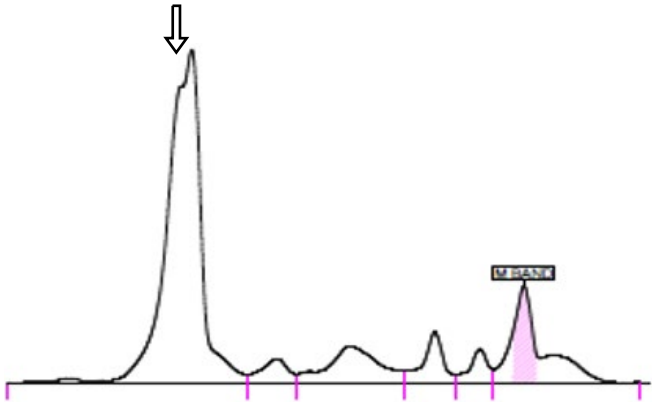

Figure 2: Electrophoretogram of Case-1 after chemotherapy showing bifid albumin peak as well as M band

Case 2:

A 48 year old male patient had complaints of backache and paraparesis. He was evaluated at outside hospital and diagnosed as plasmacytoma in the epidural region. He was treated with decompressive laminectomy with excision of epidural mass followed by 5 weeks of external beam radiation therapy to D5 – L1 vertebrae. In view of suspicion of multiple myeloma, bone marrow aspiration was done, which showed 38% plasma cells, suggestive of plasma cell neoplasm. Skeletal survey was showing multiple lytic lesions in the skull, ribs, femur, humerus and tarsal bones. He was sent to our hospital for further management. At our hospital, the results of serum creatinine, calcium and liver function tests were normal, except for high total protein of 144 g/L, high globulin and altered A:G ratio. Serum free light chain assay was suggestive of kappa type of monoclonal gammopathy. The electrophoretogram was showing a distinct M band of 67 g/L in the gamma region and the albumin region was showing two bands which were not clearly demarcated. From the investigations, he was diagnosed as multiple myeloma and was planned treatment with Lenalidomide, Bortezomib, and Dexamethasone (RVD) Regimen. Electrophoretograms of this patient (figure 3 and figure 4), later during follow up, while on chemotherapy, were all showing the same extra band in the albumin region, which was more distinct, confirming the presence of bisalbuminemia.

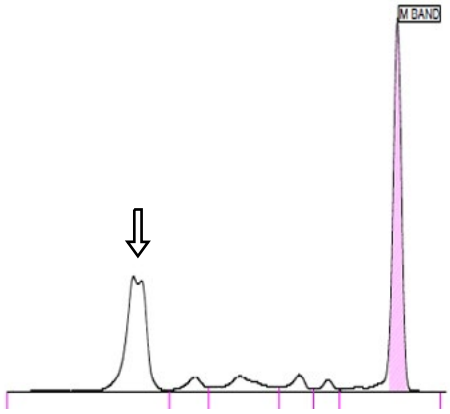

Figure 3: Electrophoretogram of Case-2 at the time of presentation showing bifid albumin along with M band.

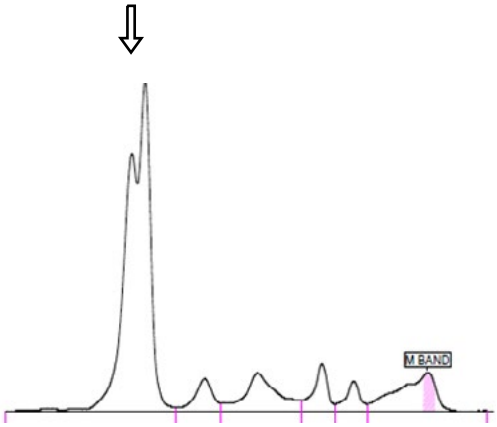

Figure 4: Electrophoretogram of Case-2 after chemotherapy showing bifid albumin peak as well as M band.

Table 1: Investigations performed at the time of presentation in both the cases.

Parameter (Units)	Case-1	Case-2	Reference range
Serum Total Bilirubin (µmol/L)	3.42	6.84	3.42 – 22.2
Serum Creatinine (µmol/L)	60.1	85.7	58.3 – 110.5
Blood Urea (mmol/L)	2.33	4.49	3.16 - 7.18
Serum Total Protein (g/L)	88	144	63 – 82
Serum Albumin (g/L)	45	50	35 – 50
Aspartate transaminase (SGOT) (U/L)	13	21	17.0 - 59
Alanine transaminase (SGPT) (U/L)	12	46	0 - 50.0
Alkaline Phosphatase (ALP) (U/L)	76	83	38 - 126
Serum Free Kappa light chain (mg/L)	112.1	145.5	3.30 – 19.40
Serum Free Lambda light chain (mg/L)	8.64	15.7	5.71 – 26.30
Free Kappa/Lambda (κ/λ) ratio	12.97	9.20	0.26 – 1.65
Hemoglobin (g/L)	48	102	130 – 170

DISCUSSION

Bisalbuminemia is an incidental finding in serum protein electrophoresis and can be identified using electrophoresis only. Bisalbuminemia is a rare disorder characterised by the presence of two distinct fractions of albumin on serum protein electrophoresis. This can be hereditary or acquired and is very uncommon in Indian population (1). As seen in our hospital, out of 3360 patients screened for plasma cell neoplasms using serum protein electrophoresis during the last five years, only two patients had the presence of bifid albumin peaks in their electrophoretograms. The prevalence of bisalbuminemia obtained in our hospital is about 0.06% indicating the rarity of the condition. Albumin variations, either acquired or inherited, should always be on the radar of both clinicians and research scientists. Such new forms can possibly provide data on protein evolution and on the molecular structure and characteristics of the albumin molecule (5). There is no known clinical significance of this finding, though this should not be misinterpreted as an abnormal globulin peak specifically when dealing with suspected or confirmed cases of plasma cell dyscrasia (10). However, some albumin variants may have altered affinity for some hormones, especially thyroxine, metal ions, fatty acids, and drugs, with clinical implication in rare scenarios(9). There is no known association or pathophysiological relationship between bisalbuminemia and multiple myeloma. The recognition of bisalbuminemia in these patients is likely simply due to the fact that serum protein electrophoresis is commonly performed in patients with suspected myelomas. The incidence in myeloma patients is expected be similar to that of the general population (8). The differential diagnosis of an additional band in the same region as albumin includes various conditions. The first among them is that the band might be an artefact of electrophoresis, which usually happens in gel electrophoresis due to air bubbles, distortions of the gel, overloading, etc. Since we have used capillary system for electrophoresis, gel artefacts can be ruled out. Bisalbuminemias are more frequently encountered with the development of capillary electrophoresis, because this technique offers better resolution (9). Secondly, proteins that normally migrate in the same region of albumin may be elevated and mimic the ap¬pearance of bisalbuminemia. These include prealbumin, which is increased after recent food ingestion, alpha 1 acid glycoprotein (an acute phase reactant), and alpha lipoproteins. Moreover, any unusual band in a serum protein electrophoresis may be a paraprotein of monoclonal gammopathy (6). In our case, no discordances were found between the spectrophotometric quantification of albumin in VITROS 5600 dry chemistry systems and the albumin concentration determined by capillary electrophoresis. Bands due to acute phase reactants and food ingestion are temporary and do not recur on electrophoretic run in several different occasions as it recurred in our patients. Paraprotein band is a separate band in the gamma region in both our patients. As the patient is on treatment for myeloma and the M band concentration have decreased, comigration of free light chains and abnormal proteins can be ruled out. Lastly, interferences by radio-opaque agents or medications, which could lead to the appearance in the capillary electropherograms of abnormal peaks, were discarded as explanations because they are visible in the α2-globulin fraction or beta region and do not show a bifid pattern in the albumin region (11). No genetic study was performed in our cases to ascertain the genetic causes of bisalbuminemia, as the primary concern of these patients was monoclonal gammopathy. In a study by Chan PC, the author found that bisalbuminemia is not associated with monoclonal gammopathies, but, is an incidental finding (8). Bisalbuminemia can interfere with the serum protein electrophoresis diagnosis, but, is of little diagnostic or therapeutic significance. This can cause difficulty in the reporting of serum protein electrophoresis diagnosis in multiple myeloma. Hence, it is important to recognise such variant, while interpreting serum protein electrophoresis (7, 8, 12). The experience and expertise in SPE reporting helps ensure the identification of even a faint M-band or spike and distinguish it from the other bands including the albumin variants (12). Moreover, learning about albumin variants can be of great inquisitiveness and might be valuable in assessing their geographical distribution.

CONCLUSION

Bisalbuminemia is an extremely rare entity encountered on serum protein electrophoresis. Its presence should be acknowledged and not mistaken for a paraprotein band, though its presence does not influence the disease process in multiple myeloma.

Authors' contribution

All the authors have contributes to the intellectual content of this paper including Conception of the idea, drafting the article, Critical revision and final approval of the version to be published.

Authors' disclosures or potential Conflicts of interest

No authors disclosed any potential conflicts of interest.

REFERENCES

1. Kapatia G, Wadhwa M, Malhotra P, Prakash G, Aggarwal R. Bisalbuminemia: A pathologist's insight of an uncommon phenomenon. Journal of Laboratory Physicians. 2021; 13(03): 219–223.
2. O'Connell, Theodore & Horita, Timothy & Kasravi, Barsam. Understanding and interpreting serum protein electrophoresis. American family physician. 2005; 71(1): 105-112.
3. Richard A. McPherson, Matthew R. Pincus. Henry's clinical diagnosis and management by laboratory methods. St. Louis, Missouri. Elsevier; 2017.
4. Mark A. Valasek, Richard T. Hopley, Frank H. Wians, Resolving the Baneful and Banal: Bisalbuminemia in an Adult With Waldenström Macroglobulinemia, Laboratory Medicine, 2008; 39(12): 723–726.

5. Chhabra S, Bansal F, Saikia B, Minz RW. Bisalbuminemia: a rarely encountered protein anomaly. Journal of Laboratory Physicians. 2013; 5(02): 145–6.
6. Angouridaki C, Papageorgiou V, Tsavdaridou V, Giannousis M, Alexiou-Daniel S. Detection of hereditary bisalbuminemia in a Greek family by capillary zone electrophoresis. Hippokratia. 2008; 12(2): 119-21.
7. Dhavale A, Bokankar D, Argade S, kale B. Bisalbuminemia: An Uncommon Finding on Serum Electrophoresis. Journal of Clinical & Diagnostic Research. 2022; 16(8): 1-2.
8. Chan PC, Yasodhara A, Truong D. Bisalbuminemia: Lack of association with monoclonal gammopathy and value-justification for reporting in serum protein electrophoresis. Journal of Clinical Chemistry and Laboratory Medicine. 2017; 1(1): 108.
9. Tarik Adioui , Hasna Igorman, Imane Radouane , Salma Ouahid, Sanaa Berrag, Mouna Tamzaourte; A Rare Bisalbuminemia Etiology: Cholestatic Hepatitis Case Report. Asian Journal of Research and Reports in Gastroenterology. 2023; 7(1): 1-5.
10. Agarwal P, Parkash A, Tejwani N, Mehta A. Bisalbuminemia: A Rare Finding on Serum Electrophoresis. Indian journal of hematology & blood transfusion : an official journal of Indian Society of Hematology and Blood Transfusio. 2018; 34(3): 558–559.
11. Jaeggi-Groisman SE, Byland C, Gerber H. Improved sensitivity of capillary electrophoresis for detection of bisalbuminemia. Clinical Chemistry. 2000; 46(6): 882-883.
12. Pavithra, H.K., Tahlan, A., Agrawal, N., & Singh, R. Bisalbuminemia: Complicating the Diagnosis of Multiple Myeloma. IAR Journal of Medical Science. 2020; 1(6): 310-311.