False bisalbuminemia and hyperalphafetoproteinemia

Fausse bisalbuminémie et hyper-alpha-fœtoprotéinémie

A. Boujelbene, I. Hellara, F. Neffati, M.F. Najjar

Laboratoire de biochimie et de toxicologie, hôpital universitaire de Monastir, 5000 Monastir, Tunisia

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Summary
The capillary electrophoresis is a very powerful separation method offering a high degree of resolution. However, certain interferences can be detected giving transitory shoulders or peaks. We report the case of a serum protein electrophoresis performed with CapillarysTM (Sebia) in a 68-year-old patient, hospitalized for cancer of the head of the pancreas, which showed an important shoulder in the migratory range of albumin, simulating bisalbuminemia. An interference with alphafetoprotein was proven explaining this electrophoretic aspect.

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Résumé
L'électrophorèse capillaire est une méthode de séparation très performante, en particulier sur le plan de la résolution. Cependant, certaines interférences peuvent être détectées donnant des épaulements ou des pics transitoires. Nous rapportons le cas d'une électrophorèse des protéines sériques réalisée sur CapillariesTM (Sebia) chez un patient de 68 ans, hospitalisé pour cancer de la tête du pancréas, qui montrait un épaulement important dans la zone de migration de l'albumine, simulant une bisalbuminémie. Une interférence avec l'alpha-fœtoprotéine était prouvée expliquant cet aspect électrophorétique.

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History
A request for serum protein electrophoresis was addressed to the gastroenterology unit for a 68-year-old man with an uneventful past history who had been hospitalized for exploration of cutaneous jaundice associated with dark urine and pale stools. The gallbladder could not be palpated at physical examination.

Routine laboratory tests showed signs of cholestasis with elevated alkaline phosphatase at 155 IU/L and gamma-glutamyltransferase (GGT) at 217 IU/L (7N). Serum transaminases were elevated at 80 IU/L (2N) for ASAT and 106 IU/L for ALAT (2,5N). Total bilirubin and conjugated bilirubin were 313 (18.4N) and 225 (45N) µmol/L respectively. Prothrombin (PT) was 53% and total protein 69 g/L. Protein electrophoresis showed a shoulder in the albumin zone, simulating bisalbuminemia: the usual albumin peak was measured at 23 g/L and the slower moving shoulder 3.9 g/L (Fig. 1a). The alphafetoprotein (AFP) level was 150,000 IU/mL (181.5 mg/L) (normal = 3.0IU/mL, 3.63 µg/L). Blood cell counts, creati-
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Figure 1 Serum protein electrophoresis before (a) and after (b) treatment with anti-AFP antibodies.

nine, uric acid, total cholesterol and triglycerides were normal.

Abdominal ultrasound showed a dysmorphic liver with a dilatation of the intra- and extrahepatic bile ducts and a distended gallbladder. The pancreas was not visualized. An abdominal computed tomography (CT) was performed and confirmed the presence of a tumor in the head of the pancreas with infiltration of the peripancreatic fat and mesenteric nodes. The classification was T1N1M0 stage III.

Diagnosis

Pseudobisalbuminemia by interference with AFP related to a pancreatic tumor.

Comments

Each of the five or six fractions of protein electrophoresis, gammaglobulins, betaglobulins (β1 and β2), alpha-2-globulins, alpha-1-globulins and albumin can produce a narrow peak, reflecting the presence of a large quantity of a unique type of protein [1]. In the albumin fraction, the presence of a second protein produces a bifid peak called bisalbuminemia.

There are two types of bisalbuminemia: hereditary familial bisalbuminemia, which is permanent, or acquired or transient forms. In general, bisalbuminemia has no pathological significance, with the exception of cases associated with a pseudo-cyst of the pancreas [1].

Detection of bisalbuminemia has become a frequent finding in medical laboratories since the routine clinical technique for electrophoresis on agarose gel or cellulose acetate has been replaced by capillary electrophoresis. This more sensitive technique discloses the anomaly previously missed by classical electrophoresis [2,3].

Hereditary bisalbuminemia results from the simultaneous presence of two types of albumin with different electrophoretic mobilities. Certain variants may exhibit affinities different from that of "normal" albumin, in particularly for the transportation of hormones, metal ions, fatty acids or drugs, which as a result have a higher blood level [4]. This situation was ruled out in our patient.

Acquired bisalbuminemia results from modifications in the structure of circulating albumin, mainly after rupture of a pancreatic cyst into a serous cavity, releasing pancreatic enzymes, which can digest part of the albumin [5]. This partial proteolysis of the native albumin by chymotrypsin and carboxypeptidases produces a modified albumin. The undigested fractions migrate differently on the electrophoresis where they produce two distinct narrow peaks. This hypothesis cannot be retained in our patient because there was no fistula or pseudocyst in the pancreas. Bisalbuminemia can also develop transiently by uptake on part of the albumin of a monoclonal immunoglobulin, for example in patients with myeloma [6]. This was not the causal mechanism in our patient. Finally, transient bisalbuminemia can result from high-dose betalactamine therapy. The two peaks are explained by antibiotic fixation on part of the albumin: the betalactame cycle opens allowing a link between its carbamyl cycle and an amine moiety of albumin lysine [1]. The peak generally appears between the third and eighth day of treatment and is more marked for higher antibiotic doses, again a hypothesis which cannot be retained in our patient who was not taking antibiotics.

Thus, in our patient, the three hypotheses explaining acquired bisalbuminemia cannot be retained. The hypothesis of biochemical interference was proposed. The most likely candidate was AFP, because of its overly high concentration and also because it migrated very close to the albumin fraction. Protein electrophoresis performed after precipitation of AFP with specific antibodies (antibodies from a kit designed for AFP assay, Cobas 6000 Roche®) and after elimination of the bilirubin interference, eliminated the shoulder effect, producing a curve, which progressively returned to normal (Fig. 1b).

Albumin assay with an immunoturbidimetric method (Integra 400, Roche®) gave 27 g/L, close to the level estimated for the rapid fraction with Capillars®. This confirms the rapid fraction as albumin and the slow fraction, the false bisalbumin, as AFP.

AFP is a 70kDa glycoprotein with a structure close to albumin. On electrophoresis, serum proteins migrates between the alpha-1 fraction and the β-globulins [7,8]. Mono-, bi-, and trimeric forms are observed, with highly heterogeneous fucosylation. Glycane chains account for 4 to 5% and, because of its similarity with albumin, it could function as a transport molecule for several different ligands such as bilirubin and fatty acids [8,9].
Elevated AFP is rare for pancreas tumors, and occurs in less than 10% of acinous cell cancers [7,9]. In the majority of cases, the concentration does not exceed 10,000 IU/mL (12,100 µg/L). A very high level is associated with hepatoid differentiation [10]. These tumors are rare and often associated with liver metastases at diagnosis [4]. AFP concentrations vary from 6 to 700,000 IU/mL (84,700 µg/L) [11]. In our patient, the AFP was mainly produced by the pancreatic tumor, which was probably hepatoid. The presence of liver metastases was not demonstrated.

The heterogeneous nature of AFP, depending on the degree of fucosylation, controls differential precipitation with concanavalin A and other lectins and could enable differentiation of AFP of hepatocellular carcinoma from that observed in benign diseases [12,13]. The exceptional migration of AFP in the zone of albumin migration, as observed in our patient, could be explained by the following hypotheses: structural and functional similarity between albumin and AFP and heterogeneous AFP fucosylation.

Conclusion

Capillary protein electrophoresis enables a reliable and reproducible analysis of serum samples. Interpretation of the electrophoresis recording differs little from that obtained with electrophoresis on agarose gels or cellulose acetate, but requires perfect knowledge of specific phenomena and skill in discerning analytical interferences.

Conflict of interest statement

There is no conflict of interest.

References