Pigment Gallstones

Pigment gallstones, i.e. stones that have a cholesterol content of less than 20% of dry weight, are of two types: brown and black stones. Brown stones, also called 'calcium bilirubinate' or 'bile pigment calcium stones', have been described from Japan and Southeast Asian countries. They occur all over in the biliary ductal system and are almost always associated with infection. They have a dull, earthy brown surface and are easily crushable. On cross section, they appear laminated, with a characteristic pattern of alternating dark (brown) and light (tan) concentric layers. In contrast, the black stones are generally multiple and dark black and are found in the gallbladder. They are not associated with biliary infection. Some of them are friable and pellucidae while others are brittle and hard. Among the black stones, there is much variation in the texture and colour as also in composition. They have thus been broadly divided into two subtypes depending on their composition: the carbonate and the noncarbonate black pigment gallstones. The noncarbonate stones may be either black phosphate or black bilirubinate stones.

The cut surface of brown stones is usually spongy and porous, with concentric rings of brown and tan. The brown layer is made of calcium bilirubinate and contains very little fatty acids, whereas the tan layer contains predominantly fatty acids, the major one being calcium palmitate. On scanning electron microscopy, the brown rings appear smooth and featureless, while the fatty acid-rich tan layers are rough with stacks of jagged plates. The microstructure of black pigment gallstones, on the other hand, is quite different and somewhat variable. The black carbonate stone is rough and granular, and the cut surface is marked with pits and granules. Often, a layering is seen. The narrow rough rings are rich in calcium and phosphorous while the wider and smoother rings are rich in sulphur. The noncarbonate stones have a smooth surface and a homogeneous cross-section. Of them the black bilirubinate stones are the most homogeneous. The phosphate stones have a somewhat rougher surface in the centre which is rich in sulphur and copper. In general, the smooth areas in pigment calculi are associated with calcium bilirubinate and a high concentration of sulphur, which is present in a low valence state such as is found in sulphide, disulphide or mercaptan linkages.

These structural and compositional differences suggest that the pigment calculi possibly form by varied mechanisms. Whilst the brown stones are believed to be the outcome of infection, the black stones are products of some metabolic abnormality. Be it haemolysis, cirrhosis of the liver or old age, in the case of brown pigment stones, the β-glucuronidase present in the bacteria infecting the bile as well as that released from the bile duct mucosa following cholangitis hydrolyses the conjugated bilirubin. The liberated unconjugated bilirubin is insoluble in bile. This binds with the cations available in the bile, the predominant one being calcium. The calcium bilirubinate and perhaps other salts of bilirubin thus produced form hydrophobic colloids sensitive to coagulation and stabilization by bile salts. The colloid stability depends on the bile salt concentration, which is lower in hepatic bile than in the gallbladder bile; hence calcium bilirubinate precipitates much more readily in the bile ducts than in the gallbladder. Such precipitation occurs either by complexing with proteins or by undergoing partial polymerization. Perhaps, in a similar fashion, bacteria release phospholipases which cleave fatty acids from biliary phospholipids; these fatty acids also precipitate as calcium salts in the stones mostly in combination with calcium bilirubinate, thus raising the possibility of their coprecipitation.

In patients with black stones, since biliary infection is absent and yet unconjugated bilirubin is present in excessive amounts in the bile, it is believed that β-glucuronidase of the gallbladder mucosa might be deconjugating the bilirubin glucuronides of the bile. It is possible that in some patients an excessive amount of unconjugated bilirubin may be secreted into the bile. Black stones are associated with haemolytic disorders or liver cell disease such as cirrhosis. Ethanol infusion has been shown to induce an increase in the biliary levels of unconjugated bilirubin in animals as well as humans. As a result it has been speculated that ethanol might have a role in the pathogenesis of black pigment gallstones.

The finding of red blood cells in the centre of a stone in the study by Rajagopal et al. reported in this issue of the Journal is reminiscent of the observations made by Been et al in their study of the microstructure of cholesterol gallstones. They had proposed that hard mineral deposits in the initial nidus might injure the gallbladder mucosa and cause microhaemorrhage, which might further promote nucleation. Similar events could presumably be occurring during pigment gallstone formation.
That the brown pigment stones occur more commonly in less developed countries and further that their frequency in these countries also has decreased possibly because of recent affluence and improved sanitation attest to the 'infective theory.' Further credence is given to it by the association of parasitic infections with 'Oriental cholangitis' from Japan, China, Hong Kong, Singapore and Korea. Also known as 'recurrent pyogenic cholangitis' and 'cholangio-hepatitis,' this condition manifests with soft brown stones in dilated biliary ducts in middle aged Orientals. Jaundice and fever are the main presenting features. Death often occurs because of renal failure or septicemia. It is believed that parasitic infection, such as due to Ascaris lumbricoides or Clonorchis sinensis, is responsible for this disease. One would expect such stones to be present in India in large numbers but they have not been reported so far, except in a recent study from Kerala where, of 64 gallstone patients operated on in a single centre over a period of 3 years, seven were found to have such intrahepatic duct stones (Philip Thomas presentation). The demonstration of ascaris in the biliary tree of many patients in Srinagar also raises the possibility that some of them might be having ductal stones.

In the relatively affluent part of the country, however, the gallstone profile is similar to that seen in the Western countries. About 80% of the gallstones obtained from cholecystectomies in Delhi and Punjab are cholesterol gallstones. The pigment stones studied and reported by Rajagopal et al from Bombay also conform to the 'Western type,' i.e., dark black stones occurring in the gallbladder.

Knowledge of the composition and pathogenesis of the black pigment gallstones is important not only because agents for dissolving them need to be developed but also because pigment is present in the centre of most cholesterol stones and may be responsible for initiating the formation of all types of gallstones. The exact nature of the black pigment or the residue of pigment stone extractions is not known. However, they all appear to be derived from bile pigments since Wosiewitz and Schroeder have demonstrated that like bile pigments they too get degraded into maltesides and pyrrolederivatives when treated with chromic acid or chromate. Calcium bilirubinate is well recognised and is found in abundance in the brown pigment stones but in proportionately much smaller amounts in the black pigment stones. In order to investigate the other possible bilirubin-metal complexes in the black pigment, we synthesised in vitro complexes with two transition metals, viz., Cu and Zn. Both these metals have been found to form stable complexes with bilirubin, maximally when placed with it in 1:1 molar ratio. Their black appearances and other characteristics suggest that they might be present in the 'improbable' black pigment which has thus been suspected to be a combination of metals, pigment and proteins. This pigment resists dissolution by the most potent organic solvents. Hence, attempts are being made to dissolve the glycoprotein matrix on which the pigment complex is laid and some initial success has been achieved in this direction by using a highly alkaline bile-acid-EDTA solution alternating with a modified glyceryl-monooctanoate preparation. Continued efforts to understand the chemistry of black pigment and the microstructure of pigment gallstones are needed before complete dissolution of all types of gallstones can be achieved.

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References