

## ANSWERS

1 Describe the features shown in pictures A, B, and C, using them to reach a diagnosis, and relating them to each other.

**A** [Picture A](#) shows a tumour plaque arising from the colonic mucosa, about four centimetres in diameter, with rolled edges and an ulcerated and partially necrotic centre, the appearances are typical of a colorectal adenocarcinoma. [Picture B](#) shows a section of a portion of lymph node (the subcapsular sinus is at the top right hand of the picture, and the band of small blue-staining cells underlying this, running diagonally from top left to bottom right represents the cortical region of the node containing lymphocytes). Within the lymph node (in the bottom left-hand quadrant of the figure), there are many irregular glandular epithelial structures. The features are therefore those of metastatic adenocarcinoma. [Picture C](#) shows two separate foci of adenocarcinoma growing within the liver. These appearances are entirely typical of metastases in the liver. The three pictures thus demonstrate a primary colorectal adenocarcinoma, which has metastasised to local lymph nodes (by lymphatics) and to the liver (by the bloodstream).

2 What common possibilities might account for the man's sudden death? How would these be disclosed by the autopsy findings, and what would the findings in the lung be? What features in the history place this patient at particular risk of such events?

**A** There are very few causes for truly sudden death. Myocardial infarction with a ventricular arrhythmia could be one, but more probable is a massive pulmonary embolus, in this case from venous thrombus in the right leg. Autopsy would distinguish between these alternatives, by revealing the large thrombo-embolus impacted in the pulmonary arteries. Because death was nearly instantaneous, the lungs would show no infarction. This patient was susceptible to venous thrombosis by virtue of the pro-coagulant reaction to major surgery and the tendency for venous stasis through inactivity post-operatively. Further, some malignant tumours may release pro-coagulant factors.

3 What does this information suggest about the nature of the abnormal colonic tissue?

**A.** The gel reveals the presence of two alleles at the tested site on chromosome 17p in the DNA from normal tissue (track N), and near-complete loss of one of these alleles from the DNA derived from the tumour (track T). This proves that the tumour is derived from a clone of cells in which a part (if not all) of the short arm of one of the copies of chromosome 17 has been deleted (the other allele is retained). Loss of one copy of 17p frequently accompanies mutation of the

oncosuppressor p53 on the other (retained) member of the chromosome pair. This is exactly as expected to provide the two-hit gene deletion expected for oncosuppressor gene inactivation. However, why 17p deletion is so frequent in colorectal cancer is not quite so simple to explain, for point mutation in *p53* alone is itself competent to interfere with the function of residual p53 protein, because the mutated p53 protein interferes with the structure of the homotetramers which are required for the biological activity of p53 protein. This is referred to as the dominant negative effect of mutated *p53*. Presumably, loss of all normal *p53* alleles creates a more profound deficiency of *p53* oncosuppressor function than this dominant negative effect.

4 In retrospect, there were serious errors of omission in the management of this case. In the light of your knowledge of the pathology involved, what were they, and what difference in outcome might have been secured had they been avoided?

**A** The most significant error was failure to explore the cause of the microcytic, hypochromic anaemia. This is the classical picture of anaemia due to chronic blood loss, in this case almost certainly from the colonic tumour. The possibility is real that the earlier diagnosis might have led to successful treatment prior to metastases. Indeed, it is theoretically possible that the colonic tumour was still in a pre-malignant adenoma phase at the time of the first visit to the general practitioner. A further potential error was failure to recognise the venous thrombosis, whose disastrous embolic outcome might have been prevented by suitable management.

5 In view of the patient's age, what further action should now be taken?

**A** Forty-two is much lower than the mean age for contracting colorectal cancer (around 70 years). This suggests that the patient may have a hereditary predisposition, and a careful family history with surveillance of the relatives would be in order.

There are two kinds of hereditary predisposition to colon cancer, adenomatous polyposis coli (APC, also known as familial adenomatous polyposis, FAP) and Lynch Syndrome (aka Hereditary non-polyposis colorectal cancer, HNPCC). Two pieces of evidence suggest that, if there is a hereditary predisposition, it will be Lynch Syndrome: (i) APC is much rarer than Lynch Syndrome (which affects of the order of 1 in a few thousand), (ii), there is no sign of polyps on the photos (the blob under the mucosa is probably a haemorrhoid), which would be expected in APC ('polyposis coli'). (Lynch Syndrome is mismatch DNA repair defect and doesn't increase the incidence of polyps much).

Sequencing the patient's constitutional DNA for APC, MLH1 or MSH2 mutations is probably not yet routinely done, but may be in the near future.