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# Hepatic Incidentaloma: A Modern Problem

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**As clinical skills give way to increased reliance on organ imaging, a new clinical problem is identified—the hepatic "incidentaloma." This may be defined as an unexpected solid filling defect in the liver of a well patient. Thirty-six such lesions have been seen in one practice over a period of 36 months. Twenty-nine (81%) were benign: 24 (67%) nonneoplastic conditions and 5 (14%) benign tumors. The remaining 7 (19%) were malignant: 5 secondary tumors and 2 primary tumors. Patients with physical signs of liver mass or enlargement were more likely to harbor malignancies. An elevated serum alkaline phosphatase (SAP) was suggestive of malignancy. Hepatic hemangioma was the most common single diagnosis (20 patients, 56%). We propose a regimen of investigation which should allow diagnosis to be reached in about one-half of these patients without admission to the hospital. The rest will need at least a short hospital admission for angiography and fine-needle aspiration biopsy.**

Clinical diagnosis has changed remarkably within a generation. The high status once given to physical examination is now accorded to testing and imaging. It is common to see patients in consultation who have been most comprehensively investigated, but who have never had a thorough history taken, nor been the subject of a proper physical examination. There is no point in bemoaning this change. We must live with it and with the problems that follow from it.

The general use of organ imaging to extend history and examination has brought to light a new class of patient who has a chance finding or "incidentaloma." A good deal has been written about [1, 2] the diagnosis and natural history of the adrenal incidentaloma, but there is little to be found about the filling defect in the liver that has been found by chance [3–6]. Yet such findings are not uncommonly made during the investigation of those obscure abdominal symptoms that are so frequent in any general or gastroenterological practice. Sometimes, these symptoms are in no way related, being situated in another quadrant of the abdomen or shifting in their site, like the pain of irritable gut. At other times, epigastric pain of an indefinite type could be related to the liver lesion. In some patients, persistent epigastric and right upper quadrant pain are much more clearly related to hepatic pathology.

This study has been undertaken to answer specific questions: What are the likely diagnoses, and how do symptoms and signs relate to the possible diagnoses? How should such patients be investigated in order to achieve a diagnosis and management plan as quickly and economically as possible? We have not attempted to make a detailed analysis of the performance of individual symptoms, signs, and investigations as predictors of diagnosis nor to discuss treatment of the various possible entities. Rather, we have been concerned with offering practical suggestions based on our interpretation of epidemiology and the use of selected clinical data and investigations.

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## Material and Methods

All patients with undiagnosed solid liver masses referred to one of the authors (J.M.L.) between October, 1985 and the end of October, 1988 have been included. Most patients arrived with both an ultrasound and computed tomography scan. Patients who had cystic or biopsy-proven lesions were excluded, together with those with lesions detected on routine follow-up after resection of colorectal primaries and those with lesions appearing during follow-up for hepatitis B. Patients were also excluded if they had a Karnofsky index of less than 80 and had a presumed diagnosis of malignancy on that basis. The patients considered, therefore, were all reasonably well and without a presumptive diagnosis of the nature of their liver lesion.

Symptoms were classified as absent or nonspecific (Grade 0), compatible with or suggestive of liver pathology (Grade 1), and specifically hepatic (Grade 2). The past history was examined for sex steroid exposure, occupational exposure to hydrocarbons and polyvinyl chloride, past hepatitis exposure, or trauma.

In the physical examination, the following details were recorded: the Karnofsky activity status, stigmata of chronic liver disease, hepatomegaly, the presence of a hepatic mass, and evidence of a relevant primary malignancy (particularly of the large bowel or rectum, breast, or melanoma).

Investigations included full blood count, MBA12 and liver function tests, hepatitis serology, carcinoembryonic antigen (CEA), and alpha fetoprotein (AFP) levels, blood pool scanning, review of ultrasound and computed tomography scans, hepatic and celiac angiography including venous phase films and fine-needle aspiration biopsy with examination of smears, cell blocks, and special staining characteristics. These tests

were not done for all patients. Investigations were terminated when there was enough information to make a diagnosis and management plan.

The lesions themselves were classified as nonneoplastic (e.g., hemangioma, focal nodular hyperplasia), benign neoplasms (that is, benign and curable but with uncertain potential for malignant change—such as hepatic cell adenoma and leiomyoma), and malignant (primary and secondary).

## Results

### *General*

Thirty-six patients who fulfilled the inclusion criteria were referred in the 36-month period under review. There was a striking preponderance of women (27 women, 9 men; chi square = 8.03, $p = 0.004$). The median age of all patients was 44.5 years.

### *Diagnoses*

Twenty-four patients (67%) had nonneoplastic lesions. Of these, 20 had hemangiomas, 14 of these being women. One woman had a large area of focal nodular hyperplasia; another had an old penetrating duodenal ulcer eroding deeply into the liver substance. A further woman had an area of localized fatty infiltration and another had a tuberculous abscess of the liver.

Five patients (14%) had benign neoplasms. Of these, 4 women had hepatic cell adenomas and 1 man had a leiomyoma of the left lobe of the liver.

Seven patients (19%) were found to have malignant lesions. Five (3 women, 2 men) had metastatic carcinoma of colorectal origin, while 2 women had primary hepatocellular carcinomas.

If the nonneoplastic lesions and benign neoplasms are grouped together, 81% of patients had benign lesions.

### *Patient Age*

The median age of patients with benign (nonneoplastic conditions and benign tumors) lesions was 41 years (range, 18–63 years). The median age of those having malignant lesions was 62 years (range, 42–71 years), a statistically significant difference ($p = 0.0004$, Wilcoxon test). There was, however, considerable overlap among the 2 groups.

### *Exposure to Sex Steroids*

Thirteen women had taken the oral contraceptive for at least 3 months within the previous 5 years. All 4 patients with hepatic cell adenoma and the patient with the focal nodular hyperplasia had taken the oral contraceptive, while only 8 of the remaining 31 patients had taken the oral contraceptive. This difference is significant ($p = 0.0034$, Fisher test). Nevertheless, exposure to the oral contraceptive offers little help with the diagnosis, since about 25% of those with diagnoses not conventionally related to sex steroids had also taken the oral contraceptive.

**Table 1.** Distribution of symptoms by grade.

| Grade | Nonneoplastic | Benign | Malignant |
|---|---|---|---|
| 0 | 9 | 1 | 0 |
| 1 | 5 | 1 | 2 |
| 2 | 10 | 3 | 5 |

**Table 2.** Distribution of physical signs.

| | Nonneoplastic | Benign | Malignant |
|---|---|---|---|
| Liver impalpable | 20 | 4 | 0 |
| Hepatomegaly | 3 | 0 | 2 |
| Hepatic mass | 1 | 1 | 5 |

### *Influence of Symptoms*

The distribution of symptoms by grade as previously defined is shown in Table 1. If all benign lesions are grouped together and patients with any possibly related symptoms are also grouped, it appears that 7 of 26 patients with symptoms were found to have a malignancy. None of the 10 patients without relevant symptoms were found to have a malignancy. This difference does not reach statistical significance ($p = 0.1547$, Fisher test).

### *Influence of Physical Signs*

Table 2 shows how physical signs were distributed between those with nonneoplastic, benign, and malignant lesions. If all benign lesions are grouped together and those who had hepatic signs also grouped, it will be seen that all 7 patients with malignant disease had physical signs related to the liver. Seven of 12 (58%) of those with physical signs were found to have a malignancy. None of those without signs had a malignant diagnosis. This difference is statistically significant ($p = 0.0001$, Fisher test).

### *Size and Number of Lesions*

Neither the size of the largest lesion nor the presence of multiple rather than single lesions was helpful in deciding whether a lesion was malignant or not. Three of the 7 patients with malignant lesions had multiple masses in the liver, compared with 9 of 29 with benign lesions ($p = 0.6639$, Fisher test). This implies that a patient with multiple lesions has about a 25% (3 of 12 patients) chance of malignancy, compared with a 17% (4 of 24 patients) chance of malignancy with a single lesion.

The median size of benign lesions was 4.2 cm (range, 1.8–10.0 cm), with that of malignant ones being 5.0 cm (range, 3.0–12.0 cm). This difference was not significant ($p = 0.4480$, Wilcoxon test).

### *Tumor Markers*

The CEA level was raised in all 5 of the patients with metastatic colorectal carcinoma. Both patients with hepatocellular carcinoma in this series had raised AFP levels.

### *Liver Function Tests*

The liver function tests analyzed included serum bilirubin, serum alkaline phosphatase (SAP), serum alanine aminotrans-

ferase (ALT) and serum gamma-glutamyl transpeptidase (GGT). Full liver function tests were not available for all patients, some of whom had screening carried out at laboratories performing different tests. Full information was available for 28 patients and only those patients were considered in this section. Gamma-glutamyl transpeptidase was elevated in 13 patients: 7 with benign lesions, 6 with malignant tumors. At least 1 liver function test was abnormal in 6 of 7 patients with malignancy and in 8 of 21 patients with benign disease. This difference does not quite reach statistical significance on Fisher testing ($p = 0.0768$). The chance of having a malignancy in the presence of one or more abnormal liver function tests was 6 (43%) of 14. Multivariate analysis showed that the SAP was the most important discriminator. Six (75%) of 8 patients with an elevated SAP were found to have a malignancy. Only 2 (10%) of 20 patients with a benign lesion had elevation of the SAP. Six of 7 patients with a malignant tumor had elevation of the enzyme.

### *Organ Imaging Investigations*

No attempt has been made to evaluate the sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of computed tomography scanning, ultrasound, angiography, or fine-needle aspiration. $^{99m}$Technetium-labelled red blood cell scanning with tomography has proved to be remarkably specific and accurate for hepatic hemangioma. It is the subject of a separate report [7]. Seventeen of the 20 hemangiomas in this series were diagnosed by this technique. Two patients were diagnosed before the technique was available in this hospital. In one, the diagnosis was not made by blood pool scanning because the lesion was too small and beyond the resolution of the technique. No false-positives were obtained.

Nineteen of the 36 patients required hospital admission for angiography and fine-needle aspiration. The diagnosis of hemangioma was completed in the other 17 as outpatients.

## Discussion

Patients presenting with a lesion incidentally found in the liver fall into 3 groups. Those with malignancy have a poor prognosis, whether the malignancy is primary or secondary [8]. Those with benign lesions that may possibly progress to malignancy (hepatic cell adenoma, leiomyoma) must either be treated by resection of the lesion or followed very carefully, if the diagnosis has been confidently made, to make sure that the lesion does not increase in size [5, 6]. A review every 6 months by ultrasound seems an appropriate routine for such patients. The third group are those with essentially harmless lesions, such as hemangioma or fatty infiltration. Such patients do not need treatment if the lesions are not causing symptoms.

In this small series, 67% of incidentally found liver lesions were shown to be completely benign and nonneoplastic. A further 14% were placed in the intermediate category of benign neoplasms with an uncertain future. It is of some comfort, then, to realize that approximately 80% of hepatic "incidentalomas" were benign. The management of adrenal lesions found in this way depends on tumor function and size [1, 2]. Size alone is of no significance in judging what should be done with a liver lesion since the sizes of benign and malignant lesions did not differ. Although patients with malignant lesions were generally older than those with benign ones, there was a good deal of overlap, and it would be wrong to depend on young age as a marker of benign disease.

Symptoms were not a reliable guide to diagnosis. It was true that malignancies were usually symptomatic and that asymptomatic lesions were usually benign. Having said that, however, it is also true that many benign lesions were symptomatic. The chance of having a malignancy in the presence of symptoms was about 27%. The presence of a palpable liver or a palpable hepatic mass was also suggestive of malignancy and 58% of those with hepatomegaly or a mass did, in fact, have a carcinoma. It must be stressed, however, that palpable mass or hepatomegaly did not automatically imply malignancy, and some 42% of patients with these signs had benign lesions.

Liver function tests are commonly said to be abnormal in the presence of malignancy, whether primary or secondary [9, 10]. This was true, but one or more of the bilirubin, SAP, ALT, or GGT were abnormal in 8 of 21 benign lesions in this series. The SAP is the test which seemed to discriminate best, and 6 of the 8 patients with an elevated alkaline phosphatase in this series were found to have malignancies. The GGT was particularly misleading. It was elevated in 13 of 28 patients for whom full liver function tests were available, and 7 of the 13 had benign hepatic lesions.

Tumor markers proved helpful in this group of patients. In prior work from this Unit, we have shown that 85% of colorectal metastases have elevation of the CEA [11]. Although the AFP was positive in both cases of hepatocellular carcinoma in this particular series, it has performed much less well in a larger series of hepatocellular carcinomas. In 34 patients previously reported, the AFP levels were found to be elevated in only 15 [12]. It was noted in that paper that AFP was only regularly elevated in patients suffering from hepatoma in the presence of hepatitis B virus infection.

It is clearly important to make a definitive diagnosis for the patient with an incidental hepatic lesion. Most patients will arrive terrified because of the possible diagnosis of liver cancer. A definitive diagnosis allows a rational discussion of prognosis with the patient as well as determining the best management for the patient. The diagnosis should be made as quickly as possible and at the lowest possible cost to the patient, the hospital, and the community. We suggest the following protocol.

As an outpatient, it is possible to arrange a full blood count and liver function tests, serological tests for AFP and CEA, a computed tomography or ultrasound, if both of these have not already been done, and a blood pool scan. All these tests can generally be obtained within a week.

The patient should then be reviewed with these results. Abnormal liver function tests (particularly, a raised SAP) must raise concern about potential malignancy. CEA is relatively specific for colorectal or other gastrointestinal primary cancer and AFP for hepatocellular carcinoma in the absence of a germ cell tumor elsewhere. Computed tomography and ultrasound will help to stage disease. A positive blood pool scan is specific for hemangioma.

If no clear answer has been obtained, or if it appears that the hepatic lesion requires surgical treatment, the patient should be admitted on a short stay basis for angiography, possibly angio-computed tomography [13] and a fine-needle aspiration if the

lesion is not obviously too vascular. Nineteen of the 36 patients in the present series required hospital admission for this phase of the investigation. Using this protocol, it is usually possible to arrive at a diagnosis within 1 or 2 weeks.

A problem, however, will remain with a few patients with small and operable lesions in whom there are no serological markers, no evidence of hemangioma, and a fine-needle aspirate that has not produced a definitive diagnosis. Where doubt exists, it is probably justified to remove the lesion. Twenty percent of incidentally found hepatic tumors will be malignant, and small size is no guarantee that the lesion is benign. In the fit patient, the mortality of such a policy would be very low, indeed. It would certainly be lower than the mortality associated with a 20% chance of failing to treat a malignant lesion.


## Résumé

Plus l'imagerie se développe, moins on se fie à la clinique et un nouveau problème clinique est identifié—"l'incidentalome" hépatique. Il peut se définir comme une lésion pleine inattendue au foie d'un patient en bonne santé. Dans notre pratique, en 36 mois, ont été vues 36 lésions de ce type. Il y avait 29 (81%) lésions bénignes dont 24 (67%) non néoplasiques et 5 (14%) tumeurs bénignes. Les 7 autres (19%) étaient malignes, 5 tumeurs secondaires et 2 primaires. Les patients ayant des signes physiques de masse du foie ou d'hépatomégalie étaient plus vraisemblablement porteurs de tumeurs malignes. Un taux de phosphatases alkalines élevé était signe de malignité. L'hémangiome hépatique était le diagnostic le plus courant (20 patients, 56%). Nous proposons une méthode d'investigation qui devrait permettre de faire le diagnostic pour la moitié des patients environ sans hospitalisation. Les autres demanderont au minimum une courte hospitalisation pour angiographie et ponction à l'aiguille fine.



## Resumen

Los avances en la imagenología diagnóstica han dado lugar a la identificación de un nuevo problema clínico: el "incidenteloma" hepático. Este puede ser definido como un no sospechado defecto de llenamiento en el hígado de un paciente asintomático. Hemos visto 36 de tales lesiones en nuestra práctica en el curso de 36 meses. Veintinueve (81%) fueron benignas: 24 (67%) de ellas no neoplásicas, y 5 (14%) tumores benignos. Las otras 7 (19%) resultaron malignas: 5 tumores secundarios y 2 primarios. Los pacientes con signos de masa hepática o de aumento de tamaño del hígado exhibieron mayor probabilidad de tener una neoplasia maligna. La fosfatasa alcalina elevada fue sugestiva de malignidad. El hemangioma hepático representó el diagnóstico más común (20 pacientes, 56%). Proponemos un proceso de diagnóstico, el cual debe permitir establecer el diagnóstico en aproximadamente la mitad de estos pacientes, sin necesidad de hospitalización. El resto requiere por lo menos una corta hospitalización para realizar angiografía y biopsia mediante aspiración con aguja fina.


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