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Case report

Chemotherapy-related persistent indirect hyperbilirubinemia

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In spite of the improvement on chemotherapy results in treating testicular cancer and the introduction of adjuvant chemotherapy to node negative (as well as node positive) breast cancer patients, there is still present a wide spectrum of early and late toxic manifestations. The combination of cisplatin, vinblastine and bleomycin given to testicular cancer might result in cariovascular, neurological, gastrointestinal and renal problems. Late effects of cyclophosphamide, methotrexate and 5-fluorouracil given to breast cancer patients might cause obesity, amenorrhea and infertility. We report a persistent asymptomatic indirect hyperbilirubinemia which was observed in two cancer patients (breast; testis) 3 and 14 months following the cessation of chemotherapy. Metastatic liver disease and involvement of other sites, as well as other causes of hyperbilirubinemia, were excluded. The exact cause of the indirect hyperbilirubinemia remained obscure.

Key words: Chemotherapy, hyperbilirubineria.

Introduction

Since the introduction of cisplatin in the treatment of germ cell tumors, survival has improved dramatically, the number of drugs used to achieve a cure has been reduced to a minimum and maintenance chemotherapy has been abandoned. Nevertheless a wide spectrum of early and late toxic manifestations still exists. The late complications are likely to develop over a long period of time. A similar problem is expected to occur in breast cancer patients after adjuvant treatment given to node positive, and recently also to node negative, patients. Direct cause–effect relationship between the chemotherapy and the toxic manifestation is difficult to prove, especially when side effects occur lately or in very low incidence and are based mainly on elimination of other etiologies related to the reported phenomenon. The aim of our paper is to report a persistent indirect hyperbilirubinemia occurring in two patients, one treated for breast cancer and the other for metastatic germ cell tumor.

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Case reports

Case no. 1

A 42 year old female underwent upper external quadrantectomy of the right breast and axillary sampling on August 1987, for a $T_2N_1(2 \text{ out of } 5)M_0$ infiltrating duct carcinoma. Her past medical history included scalp irradiation due to tinea capitis at age 6 and L_4–L_5 discectomy at age 40. Four courses of 28-day cyclophosphamide 500 mg/m^2, methotrexate 40 mg/m^2 and 5-fluorouracil 600 mg/m^2 (CMF) given on days 1 and 8 were followed by right breast irradiation (^{60}Co, tangential fields, 2 Gy × 5/week up to 50 Gy depth dose) and a boost to the scar (linear accelerator, 8 MeV electron beam, 10 fractions of 2 up to 20 Gy depth dose). A further two courses of CMF were given after completing the radiotherapy. No acute side effects were noted during the treatment. Her biochemical panel on admission to Oncology (August 1987) included protein 78 g/l, albumin 44 g/l, alkaline phosphatase 22 mU/ml, γ-GT 12 mU/ml, SGPT 18 mU/ml, SGOT 20 mU/ml, LDH 250 mU/ml, bilirubin 1 mg/dl (indirect 0.6 mg/dl). Serum electrolytes and renal function tests were all within the normal range. No significant changes in these values were observed during and just after the end of the adjuvant treatment. In April 1988, 3 months off-treatment, she develped hyperbilirubinemia of 2.8 mg/dl, of which 2.4 mg/dl were indirect. The patient was completely asymptomatic. Physical examination disclosed no jaundice of the skin or the sclera nor other signs of liver disease. Liver function tests were preserved. Liver ultrasound was normal. Normal

Coombs test excluded hemolytic anemia. Haptoglobin was above 50 g/l. Tests for the presence of Hepatitis B surface antigen, anti-HBsAg antibodies and anti-HBcAg antibodies were negative. Fasting test resulted in a 25% increase of the level of the total bilirubicin and a 29% increase in that of the indirect one. The administration of Luminal (brand of sodium phenobarbital, Winthrop Ltd) did not lower the level of the bilirubin. Urinary bilirubin level was normal. There was no clinical nor radiological or biochemical evidence for recurrent or metastatic breast cancer until September 1993. The hyperbilirubinemia persisted hitherto at the range of 2.2–3.0 mg/dl; the liver function tests remained normal. The patient refused liver fine needle biopsy.

Case no. 2

A 21 year old man, with a history of mild untreated hypertension, was admitted for evaluation of a painful mass in his left testis. Ultrasound of the testis disclosed a solid tumor. IVP, chest X rays and chest CT scan were normal. Abdominopelvic CT scan demonstrated a retroperitoneal mass at the level of the renal pelvis. LDH level was 821 mU/ml, α-fetoprotein was 0 ng/ml, β-HCG was 0 U/ml, urinalysis was normal, all other biochemical tests were within the normal range, including bilirubin, serum proteins and liver function tests. In February 1986, he underwent left orchiectomy followed by laparotomy and retroperitoneal lymph node dissection. Embryonal carcinoma was found in the testis and in the retroperitoneal bulky lymph nodes. Postoperative imaging did not demonstrate any residual disease. Biochemical tests were all within the normal range, including total bilirubin level of 0.75 mg/dl. Four courses of 28-day cisplatin 20 mg/m^2 on days 1–5, vinblastine 0.15 mg/kg on days 1 and 2, and bleomycin 30 mg weekly for 12 weeks (PVB) were administered till July 1986. On January 1987 there was no evidence for recurrent disease. The liver was palpated 3 cm below the costal margin on the midclavicular line, and was soft and non-tender. Liver function tests and bilirubin level were normal. CT scan of the liver demonstrated a normal-size homogeneous liver. No disease was evident at that time. On September 1987, the bilirubin level was 1.8 mg/dl, of which 1.6 mg/dl was indirect. Liver functions remained normal. On December 1987, the bilirubin level increased to 2.5 mg/dl, of which 2.2 mg/dl were indirect. The patient was completely asymptomatic. No jaundice was evident in the skin or the sclera. Complete blood count and blood smear were normal. Chest X-rays and abdominopelvic CT scan did not show recurrent disease. Liver function tests, serum iron and B12, haptoglobin level, serologic tests for HBsAg, anti-HBsAg antibodies, HBcAg, antihuman globulin (Coombs test) and urinalysis were normal. Severe peptic complaints indicated gastroscopy, which demonstrated a hiatal hernia and mild gastritis. There was no occult blood in the stool on three consecutive tests. Fine needle liver biopsy was normal. The hyperbilirubinemia and the normal other biochemical tests persisted until the report of this case, for 8 years.

Discussion

Long-term morbidity in patients with metastatic malignant germ cell tumors treated by cisplatin containing combinations such as cisplatin, vinblastine and bleomycin was reported by Fossa *et al.*[1] The late toxic manifestations occurred in 17 out of 46 long-survivors. Out of the 26 with late sequelae, five had peripheral neuropathy manifested by paresthesis, Raynaud's-like symptoms or muscle weakness. Five patients had gastrointestinal problems such as diarrhea, weight loss, intolerance for special food, chronic gastritis and recurrent peptic ulcer or diffuse abdominal pain. Three patients, who had received abdominal irradiation following the chemotherapy developed intestinal obstruction necessitating surgical intervention.[1] Two patients had angina pectoris. It has already been published that hypercholesterolemia and overweight may be risk factors for cardiovascular disease in such patients, especially the younger ones.[2] One pateint out of 26 developed hypertension,[1] one venous thrombosis in the left lower limb,[1] and elevated serum creatinine,[1,3] one Boeck's sarcoid with multiple lung densities,[1] one tinnitus,[1] five psychosocial problems related by the patients to their disease, such as alcohol abuse, inability to perform income-producing work,[1] and three new testicular cancer within 2–4 years following the complete remission. The second testicular primaries were seminoma in one case and non-seminoma in the others.[1] The threat of acute leukemia as a second primary malignancy, related to etoposide and radiation treatment, is relatively small.[4,5] Hyperrenimemia, hyperaldosteronemia and hypomagnesemia were also reported in cisplatin-treated patients.[3]

Stoter *et al.* also reported their results of long-term follow-up in similar patients.[6] Elevated serum creatinine above 1.4 mg/dL or an increment of at

least 20% above the first year's average was used as an indicator for renal failure. Twelve out of 91 patients (21%) showed relative increments of 24–93%. Two other patients, without any previous history of ischemic heart disease, died of acute myocardial infarction while on complete remission. Diastolic blood pressure over 95 mmHg was measured in 18% of patients. Three of these patients had also renal failure. Raynaud's phenomenon was reported in 23% of patients. Fifty four percent reported a deterioration in physical fitness, easy fatigability, muscle weakness or paresthesia. Peripheral polyneuropathy occurred in 68% of patients, ototoxicity such as hearing loss with or without tinnitus in 25%. Deterioration in sexual life was reported by 40%, including decreased libido, erection difficulties and ejaculation disturbances. The data regarding fertility and semen quality is incomplete.[6]

Cisplatin is a rare cause of hepatic toxicity such as steatosis and cholestasis at a standard dose.[7] At high doses, it has been reported to produce elevation of SGOT and SGPT.[8] There is a single case report of an increase density of the liver in CT scan.[9] Vincristine is primarily excreted by the liver. Hepatotoxicity related to its use is very rare.[10]

Heptatic toxicity occurs at a very low incidence in patients treated with bleomycin and could not be specifically attributed to the drug.[11]

Long-term effects of adjuvant CMF given to breast cancer patients include obesity, amenorrhea, infertility[13] and hepatocellular necrosis.[10] Both abnormal liver function tests and focal defects on radionuclide scans have been produced by adjuvant chemotherapy, proven histologically to result from severe inflammation.[13]

Hepatotoxic late effects of methotrexate include impaired function tests (elevation of lactate dehydrogenase, transaminases), parenchymal necrosis and cirrhosis.[10,14] Such hepatic disturbances have only rarely been reported after the administration of cyclophosphamide or 5-fluorouracil although both drugs are either activated or catabolized in the liver.[10] Diffuse hepatocellular destruction or massive hepatic necrosis were reported in single cases.[15,16] Hepatic veno-occlusive disease was reported after administration of cyclophosphamide.[17] Hepatotoxic manifestations are better documented after the use of busulfan, chlorambucil, dacarbazine, nitrosoureas, 6-mercaptopurine, antibiotics, plant alkaloids and others.[10] Severe hepatocellular injury at standard dose of etoposide was reported in three cases.[18] At high dose, hyperbilirubinemia, elevated transaminase and augmented alkaline phosphatase were observed 3 weeks following the administration of the drug. These cleared completely after 12 weeks.[19,20]

Hyperbilirubinemia was reported as a part of a new syndrome, comprising ascites, hypoalbuminemia, cholestasis, prolongation of the prothrombin time and elevation of transaminase in patients with metastatic colorectal cancer treatment with 5-fluorouracil modulated by *N*-phosphonacetyl-L-aspartate (PALA).[21] Peak bilirubin levels ranged from 6.84 to 27.36 mmol/l. The mechanism responsible for this syndrome was not clear. It was postulated that there was inhibition of bilirubin glucuronidation, resulting in jaundice.[21]

To the best of our knowledge, long-standing indirect hyperbilirubinemia has not yet been reported as a sequela of combination chemotherapy such as CMF or PVB. In our patients the indirect hyperbilirubinemia appeared 3 and 14 months after the cessation of the treatment. Since no other liver function tests nor any of the performed ancillary diagnostic tests were impaired, and no other acute or chronic diseases were evident in our patients, the permanent indirect hyperbilirubinemia was attributed to the previous chemotherapy.

The question whether this phenomenon is rare or whether it was not observed hitherto because it was not measured is, in our opinion, not relevant, because it is mandatory in all our cancer cases to undergo an annual complete biochemical evaluation. These were the only two patients who developed 'Gilbert's-like' disease among thousands of patients treated in our department during the last 28 years for breast cancer and dozens of patients treated for testicular malignancies. We have no explanation for this phenomenon as liver biopsy was normal in one case and refused in the second.

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