Correspondence

Pentoxifylline in Severe Alcoholic Hepatitis: A Prospective, Randomised Trial

Sir,

Regarding the article published in May 2012 “Pentoxifylline in Severe Alcoholic Hepatitis: A Prospective, Randomised Trial” in the study we have found that randomization was biased:

1. In the control group the mean creatinine was 3.0 where as in test it was 1.2 i.e. pt in control group have already deranged renal function which is one of the important cause of mortality in alcoholic patients.
2. In result they mention that the major cause of mortality benefit is due to prevention of HRS.

According to us this study is biased in terms of RFT and honorary editor should review it and do needful.

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Reply from Author

Sir

We thank Dr. Joshi et al for reading our article with interest. However, the concern expressed by them regarding randomization in this study is invalid. Patients in our study were randomized into 2 groups using sequentially numbered sealed, opaque envelopes. The numbers were generated using a table of random numbers. This method excludes any chance of bias during randomization.

Further, though the baseline median values of serum creatinine in the pentoxifylline and control groups were 1.2 and 3.0 respectively, they were not significantly different from each other, as clearly indicated by the p value of 0.07 in the Table 1. After 4 weeks of treatment, serum creatinine significantly decreased in the PTX group (p=0.00) but not in the control group (p=0.078) (Table 1 in this article). Also, PTX group showed a significant reduction in the number of patients having renal dysfunction at the end of therapy as compared to controls (PTX group 10/25 and 1/18, p=0.014; controls 13/25 and 5/14, p=0.504). Renal failure was the cause of mortality in 20% (1/5) patients in PTX group, and 70% (7/10) patients in controls (p=0.11). Therefore, we mentioned under ‘discussion’ that the better survival rate in PTX group was associated with improvement in renal functions, although the mechanism by which PTX prevents renal failure needs further research.

Reference


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Sarcomatoid Hepatocellular Carcinoma with Bilateral Adrenal Metastases

Sir,

Carcinomas with spindle cell components are uncommon neoplasms. They have been reported in many organs including the esophagus, upper aerodigestive tract, stomach and gallbladder[1]. Most hepatic tumors with sarcomatous features are sarcomatoid carcinomas as true hepatic sarcomas are rare. Sarcomatoid hepatocellular carcinoma (HCC) is a rare neoplasm, incidence of which is only 1.8% in surgically resected specimens and 3.9 -9.4% in autopsy cases[2]. We report an unusual case of sarcomatoid HCC with bilateral adrenal metastasis.

A 70 year old male, chronic alcoholic was admitted with history of pain and distension of abdomen since one day and 5-6 episodes of hematemesis 15 days back. The laboratory data –SGOT/SGPT – 105/30 IU, Total bilirubin-1.8mg%, Direct bilirubin-0.8mg%, and Alkaline Phosphatase– 134 IU. HbsAg and HCV - negative. CT abdomen and gross examination revealed micronodular cirrhosis and a well-defined 4X3 cm unencapsulated grayish white, solid, firm tumor mass in the right lobe. Both adrenals were 4X4cm each and on cut section normal architecture was completely effaced by a gray white, fleshy mass with areas of hemorrhage and necrosis, suggestive of metastasis, (Figure 1). Histopathological examination of liver sections showed a tumor composed of haphazardly arranged spindle cells with oval to spindle pleomorphic nuclei, prominent nucleoli and atypical mitosis. On thorough sampling of the liver, an area showing trabecular, acinar and pseudoglandular pattern of classical HCC was seen (Figure 2a and b). Transitional area between carcinomatous and sarcomatoid patterns was observed. Surrounding liver showed features of alcoholic micronodular cirrhosis. Sections from both the adrenals showed pleomorphic spindle cells arranged haphazardly or in a partial storiform pattern with desmoplastic stroma (Figure 3). Periodic acid

Fig. 1: Right and left adrenal shows effacement by grayish white tumor mass
have indicated that the sarcomatous component is derived from dedifferentiation or anaplasia. Some reports have interpreted HCC with a sarcomatous appearance as a double cancer i.e. HCC and hepatic sarcoma. The following evidences suggest that spindle cell HCC represents a sarcomatous differentiation from epithelial malignancy rather than a combination of HCC and sarcoma: extremely low incidence of primary sarcoma of the liver, presence of transitional features from conventional HCC to spindle cells component and high incidence of vimentin expression in the spindle cell component.

The presenting case was predominantly composed of spindle cells with focal area showing trabecular pattern. Most of the pleomorphic spindle shaped cells expressed both vimentin and keratin. Therefore the tumor was probably epithelial in origin and then transformed to one showing predominantly sarcomatous component. Also as the tumor did not express biliary epithelial markers such as CK19 and CEa, it is suggested that the tumor arose from hepatocytes rather than bile duct epithelium. Kinjo et al. suggested in their experimental model that vimentin increased when an epithelial tumor exerted a sarcomatous change. Most of the extrahepatic metastasis have spindle cell component, therefore it is believed that the spindle cell components are truly neoplastic and have a high neoplastic potential.

On immunohistochemistry the tumor cells reacted positively only with High molecular weight cytokeratin and vimentin (Figure 2c and d). The immunohistochemical stains for CEA, desmin, S-100, CD31, CD68, CK7, and CK20 were negative. A diagnosis of Sarcomatoid hepatocellular carcinoma with bilateral adrenal metastasis was made. Clinically, HCCs with sarcomatous appearance do not differ from conventional HCC with regard to age and sex distribution. The pathogenesis of the sarcomatous appearance of HCC has not yet been clarified. Most investigators have indicated that the sarcomatous component is derived from dedifferentiation or anaplasia. Some reports have interpreted HCC with a sarcomatous appearance as a double cancer i.e. HCC and hepatic sarcoma. The following evidences suggest that spindle cell HCC represents a sarcomatous differentiation from epithelial malignancy rather than a combination of HCC and sarcoma: extremely low incidence of primary sarcoma of the liver, presence of transitional features from conventional HCC to spindle cells component and high incidence of vimentin expression in the spindle cell component.

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References

2. Jae H, Young NP, Woo HJ, Hoon SC, Chani P. A Case with

Fig. 2: (a) Normal liver parenchyma at right corner [arrow], with a tumor (H and E stain, 100X). (b) Tumor showing glandular and trabecular pattern, (H and E stain, 400X). (c) Pleomorphic spindle cells, arranged in fascicles, (H and E stain, 400X). (d): IHC (vimentin) –Strong positivity in the tumor cells, (400X). (e) IHC (Cytokeratin) –Focal positivity in the tumor cells, (400X).

Fig. 3: Section from adrenal gland showing pleomorphic spindle cells arranged in short fascicles, (H and E stain, 100X). Inset - Higher magnification of tumor showing pleomorphic nuclei, (H and E stain, 400X). 

schiff and alcin blue stains did not reveal intracellular or extra cellular mucin.
Sir,

Gall bladder carcinoma is the 5th most common carcinoma of digestive tract. It accounts for 3% to 4% of all gastrointestinal tumor. Approximately 80% of gall bladder carcinomas are adenocarcinomas. They usually present with abdominal pain (80%), diminished or loss of appetite (65%), weight loss (60%), jaundice (50%) and less commonly have been found to be associated with paraneoplastic syndromes which include panniculitis-arthritis-eosinophilia, dermatomyositis, Troussseau’s syndrome, Cushing’s syndrome and leukaemoid reaction etc. Paraneoplastic syndrome refers to the disorders that accompany malignant tumors but are not directly related to mass effects or invasion by the primary tumor or its metastasis. These disorders arise from tumor secretion of hormones, peptides, or cytokines from immune cross – reactivity between malignant and normal tissues. Cytokines implicated in this process may lead to leukaemoid reaction which refers to a reactive leucoctyosis. Leukaemoid reaction has been described commonly in associations with lung, gastrointestinal, genitourinary, head and neck causes and has rarely been described in association with gall bladder carcinoma.

We are reporting this case of poorly differentiated adenocarcinoma of gall bladder with leukaemoid reaction along with a brief review of literature.

A 68 years old man presented with history of fever with weight loss of 2-3 Kg and pain in right hypochondrium for 3-4 months. Fever was mild to moderate almost continuous for more than 3 months in spite of empirical antibiotic treatment. Appetite was diminished. He was mildly anemic with average built and health. Abdominal examination revealed liver enlargement with irregular and mass like feeling. Haemoglobin was 9.1gm%. Total leucocyte count was – 57,900/, polymorphs 90%, lymphocytes 08%, eosinophils 1%, monocytes 1%, no basophils or immature cells. Platelet count –5.09lakh/cumm. Previous records also revealed polymorphonuclear leucoctyosis (P-85-90 % with occasional myelocytes and metamyelocytes). General blood picture revealed normocytic normochromic anemia with no other specific findings. Blood sugar (random), serum urea, serum creatinine and serum bilirubin were 93.00, 77.00, 1.00 and 0.30 gm/dl respectively. SGOT and SGPT were 60.00 and 93.00 IU/L respectively. Serum sodium and serum potassium were 137.00 and 4.50 mmol/L respectively. PT was 20.8 sec (control - 15.0 sec). APTT was 32.00 sec (control - 32.0 sec). Bone marrow aspiration study showed hypercellular marrow with marked hyperplasia of leukopoietic series with predominance of mature polymorphs and myelocytes and meta-myelocytes in normal proportion. No abnormal cells or excess of blast were seen (Figure 1). He was non-diabetic with sterile urine and blood culture. Widal test and malarial antigen were negative. Leukocyte alkaline phosphatase score was high suggesting a non-malignant myeloproliferative process. Alfa fetoprotein was 2.5 ng/ml. Chest X-ray was within normal limit. Ultrasonography revealed hepatomegaly with mass in right lobe of liver and gall bladder was not clearly visualized. CECT abdomen showed large heterogeneously enhancing soft tissue attenuation mass not separated from gall bladder – possibility of carcinoma gall bladder with hepatic infiltration/metastasis (Figure 2). FNAC from mass revealed predominantly...
singly scattered neoplastic cells along with occasional clusters in the background of abundant necrosis suggestive of poorly differentiated adenocarcinoma possibly from gall bladder (Figure 3). The patient had monetary constrained and he refused any further investigation.

On the basis of clinical, radiological and cytological findings a final diagnosis of “Leukaemoid reaction (paraneoplastic syndrome) in adenocarcinoma of gall bladder” was made.

The present case of carcinoma gall bladder manifested as pyrexia of mild to moderate intensity, continuous in nature and associated with raised leucocytes count with polymorphonuclear predominance (TLC-57,000/cmm, P90%). This can be said to be probably growth factor-driven paraneoplastic manifestation, a rare finding usually seen in cases with lung, gastrointestinal, genito-urinary etc but rarely with carcinoma gall bladder.

Three mechanisms responsible for leukaemoid reactions in cancer patients have been proposed: extensive tumor metastases to the bone marrow, necrosis of the tumor mass, and production of cytokines by the tumor cell such as colony-stimulating factor (G-CSF), capable of stimulating proliferation and differentiation of bone marrow cells.\(^5,^6\) Previous reports have mentioned that a single dominant cytokine produced by the tumor was responsible for the leukaemoid reaction, but Suzuki et al\(^7\) found increases in the levels of multiple cytokines in tumor culture supernatants. Kitamura et al\(^8\) could not correlate the degree of tumor necrosis with severity of granulocytosis but was unable to rule out the possibility of extensive necrosis of tumor cell to produce granulocytosis. Okuda et al\(^9\) reported five cases of hepatocellular carcinoma associated with tumor necrosis, pyrexia, and leukocytosis.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is detectable in tumor extracts or conditioned media of malignant cells from patients with leukaemoid reactions, with or without a detectable level of GM-CSF in serum. GM-CSF functions as a paracrine hormone to stimulate hematopoiesis in local areas.\(^5,^6\) Another cytokine IL-1α and IL-6 may function as paracrine hormone which is raised in large amount in areas of extensive tissue injury i.e. local necrotic area. Both of these cytokines can induce acute phase reactants and a febrile reaction. These cytokines can also induce further production of cytokines by immune reactive cells, both through a cascade mechanism and by auto amplification. We can say that the leukaemoid reaction and clinically evident fever in this case might be due to IL-1α and IL-6 production by the tumor which involved more production of cytokines in the local necrotic area. The large amounts of cytokines produced by a tumor and the local necrotic lesion are released in the peripheral blood, stimulation of bone marrow cell production resulting in a leukaemoid reaction.

We conclude that poorly differentiated adenocarcinoma of gall bladder with extensive necrosis can also manifest as pyrexia with leukaemoid reaction - a rare association and is probably due to production of multiple cytokines from a tumor and its necrosis.

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References


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