HISTOPATHOLOGY OF ENZOOTIC BOVINE HAEMATURIA IN THE DARJEELING DISTRICT OF INDIA

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SUMMARY

Enzootic bovine haematuria of the Darjeeling district of India was identified histologically as "haematuria vesicalis bovis", with the main lesions occurring in the urinary bladder. The lesion was one of carcinoma of the transitional epithelium. The transitional epithelium was grossly hyperplastic, and solid cords of transitional epithelium invaded and infiltrated into the submucosa producing transition-cell islets or nests, causing tissue reaction in the form of marked fibrosis, hyperplasia of lymph nodes, and proliferation of venules of the lamina propria to resemble haemangiomatous conditions. Haemorrhage was observed to have occurred from these lesions via lenticular ulcers in the mucosa, and this gave rise to haematuria.

INTRODUCTION

Bovine haematuria occurs in the hills of the Darjeeling district and in the contiguous hills of Nepal, Sikkim and Bhutan. It was first reported in India by Kerr (1925). It is a condition in cattle characterized clinically by the passage of fresh blood in the urine. The disease is enzootic in damp wooded upland areas in many parts of the world (Datta, 1952). It affects only adult cattle in good health, irrespective of breed and sex, and runs a chronic course. Haematuria is intermittent at first, but as the case advances it becomes continuous. The urine also contains albumin, sugar, casts, pus and bacteria. There is no febrile reaction, and the animal dies in about 3 years by which time there is marked anaemia and cachexia. There is no anorexia at any stage. The condition is incurable (Nandi, 1954).

Material

Material for study was obtained from over 100 post-mortem examinations conducted between 1952 and 1968.

RESULTS

Macroscopic findings

Gross lesions occurred only in the urinary bladder. These consisted of a generalized thickening of the entire wall with marked epithelial thickening of the mucous membrane, and small lentil-sized flat-topped eroded haemorrhagic ulcers concealed in the mucosa. The mucous membrane of the urinary bladder was further thrown into folds forming irregular ridges and crypts. The kidneys did not reveal haemorrhagic spots to account for haematuria symptoms,
although they were pale, swollen and parboiled in appearance, as in toxic degenerative changes, with an occasional cicatrix in the cortex, while the medulla was soft and red. The ureters were invariably fibrosed, thickened and coiled in appearance.

Microscopic findings

Sections of the urinary bladder stained with haematoxylin and eosin showed the following:

1. Diffuse thickening of the entire wall of the bladder.
2. Generalized hyperplasia of the transitional epithelium of the mucous membrane.
3. The mucous membrane was thrown into ridges which in section appeared conical or papillomatous in form, projecting into the lumen of the bladder. These projections were made up of grossly hyperplastic transitional epithelium in which the connective tissues of the submucosa projected and formed a core.
4. The individual cells of the transitional epithelium were grossly enlarged and had a malignant appearance with vacuolation and hyperchromatic nuclei.

Epithelial hyperplasia resulted in considerable cellular additions upwards.

5. Basal cell proliferation and the downward penetration of these through the basement membrane to structures in the lamina propria, especially in areas adjacent to the crypts of the epithelium, produced carcinomatous infiltration of transitional epithelium into tissues immediately subjacent to it, in the form of solid cords, or trabeculae. These solid cords appeared as islands or transition-cell nests.
6. The transition-cell nests were situated in the lamina propria of the submucosa and resembled the characteristic cell nests in epitheliomas and squamous carcinomas.
7. Similar hyperplasia with vacuolation of epithelium near the surface resulted in acini-like structures being formed.
8. Areolar tissues of the lamina propria revealed irregularly distributed patches of venous proliferations presenting a haemangiomatous appearance, which communicated with the lumen of the urinary bladder via small lenticular areas of ulceration in the mucous membrane, from which there was a constant loss of fresh blood into the urine.
9. The reaction in the underlying lamina propria, submucosa and muscularis as a result of carcinomatous infiltration of the hyperplastic transitional epithelium, consisted of the following changes:
   (i) Gross fibrosis of areolar and submucous conective tissue layers, with the collagen fibres and fibrous tissues running in all directions.
   (ii) Gross stimulation of the submucosal lymph nodes, and proliferation of the resulting primitive type lymphocytes around the penetrating epithelial cords or trabeculae and consequently around the transition-cell nests or acini.

(ii) The gross proliferation of the venules of the lamina propria to almost haemangiomatous proportions could be considered as a part of the reaction, ultimately proving to be the main cause of malignancy.

11. The histology of the kidneys did not reveal any gross areas of active hyperplasia, or of haemorrhage. The toxic and degenerative changes were
PLATE I

Figs 1 and 2 Hyperplastic changes of transitional epithelium and fibrous of the wall of the urinary bladder of bovines H&E × 150

Fig 3 Papillomatous growth with hyperplasia of transitional epithelium and heavily fibrous and vascularized lamina propria forming the core H&E × 60

Nandi, Br vet J (1969), 135, 11
PLATE II

Fig 4 A lymph node in hyperplasia in the submucosa. H&E x 60

Fig 5 Hyperplastic transitional epithelial cells grossly enlarged into cystic stage, also sections of infiltrating transition cell trabeculae forming "islets", or "transition cell nests". H&E x 60

Fig 6 Papilliform projections of the mucous membrane with cancerous hyperplasia of transitional epithelium, and new lymph nodes commencing into action in the submucosa in hyperplastic form below one crypt. H&E x 60

Fig 7 Swollen, vacuolated and cancerous transitional epithelial cells with hyperchromatic nuclei. H&E x 240

Nandi, Br vet J (1969), 125, 11
Fig 8 Hyperplasia of the venules of the lamina propria to haemangiomatus conditions, with transition epithelium eroded H&E X 60

Fig 9 A transition cell nest in the lamina propria H&E X 60

Fig 10 A transition cell nest magnified, showing hyperchromatic and grossly enlarged nuclei H&E X 240.

similar to those found in nephritis of infectious origin and did not appear to bear any relation to the haematuria. The urine findings were consistent with these changes in the kidneys.

12. The ureters revealed hyperplasia of transitional epithelium with gross fibrosis of the lamina propria and submucosa, ultimately involving the muscular layer.

13. Metastatic spread could not be demonstrated in the ureters.

DISCUSSION

The main lesion reported here is identical to that described in "transitional epithelioma"—a malignant cancerous condition, which Pammukcu (1955, 1957) identified in bovine haematuria in Turkey. This observation was subsequently confirmed by Olson (1959). Sofrenovic, Bratanovic & Stamulovic (1962) observed the same cancer in bovine haematuria in Bulgaria, and Suzuki (1964) has described the same histopathology in bovine haematuria in Japan.

The grossly hyperplastic epithelium suggests the presence of potent carcinogenic stimulation of the urinary bladder mucosa via the urine, so much so, that the transition cells undergo oncogenic mutation.

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Histopathologie de l'hématurie enzootique des bovins dans le district de Darjeeling, en Inde (Naundi)

Résumé. L'hématurie enzootique des bovins dans le district de Darjeeling, en Inde, fut identifiée histologiquement comme "haematuria vesicalis bovis", les lésions principales apparaissant dans la vessie. La lésion était de cancer de l'épithélium de transition. L'épithélium de transition était grossièrement hyperplastique, et des cordons solides d'épithélium de transition envahissaient et s'infiltraient dans la sous-muqueuse, produisant des îlots ou des nodules de tumeur, engendrant une réaction des tissus sous la forme de fibrose marquée, d'hypertrophie des nodules de la lymphue et de prolifération des veinules de la lamina pro prae. Il se peut à raisonner à des conditions hémangiomeuses. On observe qu'une hémoro-
Die Histopathologie der enzootischen Hämaturie beim Rind in dem indischen Bezirk Darjeeling


Histopatologia de la hematuria bovina enzootica en el distrito de Darjeeling de la India

Resumen. La hematuria bovina enzootica del distrito de Darjeeling de la India se identificó histológicamente como "haematuna vesicalis bovis", convirtiendo las lesiones principales en la vejiga urinaria. La lesión fue una de carcinoma del epitelio de transición. El epitelio de transición era densamente hiperplastico, y tendones sólidos del epitelio de transición invadieron y se infiltraron en la submucosa produciendo áreas de células de transición y más, causando reacción del tipo en la forma de linfomas, hiperplasia de los nódulos de la linfa, y proliferación de las venulas de la lamina propia que se asemeja a con- condiciones de hemangiomatosis. Se observó que la hemorragia ocurrió como consecuencia de estas lesiones via diversas fístulas en la mucosa, y esto dio lugar a la hematuria.