

## Primary Malignant Melanoma of the Gallbladder

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*Summary.* A primary malignant melanoma of the gallbladder in a 44-years-old man is presented. The typical pathologic findings in the now eight reported cases are analysed. The clinical course of the present case was determined by multiple metastases to the brain. The histogenesis of these rare tumors of the gallbladder is still obscure.

*Key words:* Gallbladder — Malignant melanoma.

Primary malignant melanomas of the gallbladder are extremely rare and usually only diagnosed in the post-mortem examination (Wieting and Hamdi, 1907; Rosenthal, 1931; Pauter and Gallavan, 1951; Thayer et al., 1955; Jones, 1961). Only in two cases was the diagnosis made prior to death (Walsh, 1956; Raffensperger et al., 1963).

The present study consists of a report of an additional case of this unusual disease. A review and analysis of the typical pathologic findings from the seven previously reported cases are presented.

### Case Report

A 44-years-old workman with a history of alcoholism was admitted to the Neurological Department of the Medical School of Lübeck on 26 December 1974 suffering from epileptic fits of the Jacksonian type affecting the right leg and arm. The attacks commenced a few weeks before admission and became as frequent as 1–2 times per week.

For one year he had suffered from headaches; in the last few months he felt sleepy, apathetic, and was temporarily confused. On physical examination a slightly enlarged liver was palpated. The neurologic investigation revealed a facial paresis and slight hemiparesis with Babinski's sign on the right side. Blood pressure was 130/80 mm Hg and pulse rate 76/min. Laboratory tests were normal except for E.S.R. at 38/82 mm. In CSF 11/3 cells and protein content of 67.2 mg% were found. EEG showed slow waves in the right parietotemporal region. On pneumography the right lateral ventricle was not demonstrated, an enlarged left one was visible. Brain scanning with  $^{99}\text{Tc}$  detected three small homogenous radioactive foci in the right parieto-occipital region. Furthermore, a fourth focus was found close to the sinus transversus. Bilateral carotid angiography revealed many small foci of increased vascularity with abnormal vascular pattern disseminated in parietal regions of both hemispheres, in the precentral gyrus on the right and near to the carotid syphon. Extensive examination for a primary tumor somewhere was negative. The patient's condition deteriorated rapidly, he became somnolent, unconscious, and died with central breath paralysis on 24 January 1975.

The necropsy (039/75) confirmed the presence of multiple metastatic dark brown tumors in the brain. The gallbladder was distended and measured  $9.5 \times 5.5 \times 1$  cm. When opened, the gallbladder was found to contain about 20 cc of viscous greenish dark brown bile. Attached to the wall of the middle region were two yellowish-brown closely located, though separate polypoid tumors measuring  $2 \times 1.5 \times 1.3$  cm and  $2.2 \times 1.4 \times 1$  cm (Fig. 1). The right adrenal showed a small pigmented tumor. No other pigmented or unpigmented tumors were found in the skin, meninges, eyes, or other visceral organs.



Fig. 1. Gallbladder showing two dark pigmented polypoid tumors

Microscopic examination revealed a partly necrotic pigmented malignant melanoma in the brain and also in the right adrenal. A small lymph nodule of the liver hilus showed a few melanotic tumor cells in the marginal sinus. Examination of the gallbladder tumors revealed a partly necrotic malignant melanoma projecting into its lumen and invading the wall of the gallbladder (Fig. 2). Both tumors were connected by lymphatic spread. The stalk is composed of irregular-shaped cells varying in size. Other cells are polyhedral or cuboidal anaplastic tumor cells with pseudoalveolar formations separated by thin, fibrous septa, sometimes with capillaries. Numerous clumps of melanin-containing cells are found scattered throughout the tumors (Fig. 3). The pigment gives a positive blackbrown color with both Masson-Hamperl's stain and Fontana's stain and a negative reaction for iron. At the base of the pedicle of both tumors, there is invasion of the muscularis with tumor cells. The muscular layer is in places interrupted by nodular or diffuse extension of the tumor cells. The submucosa is thickened below the base of the tumor.

The diagnosis is primary malignant melanoma of the gallbladder with metastatic spread to the right adrenal, lymph nodule of the liver hilus, and mainly to the brain.

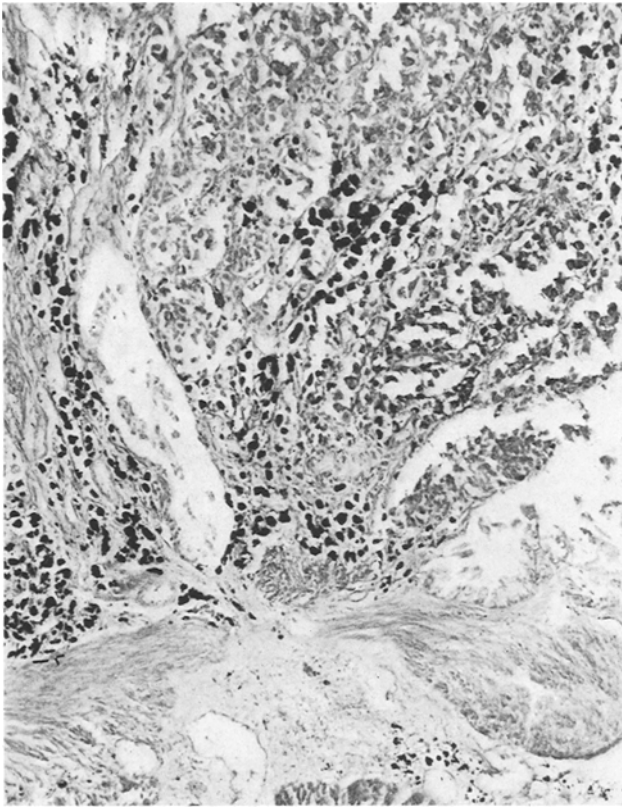


Fig. 2. Anaplastic tumor cells with pseudoalveolar formation and thin fibrous septa. Invasion of the muscularis with tumor cells. Masson-Hamperl's stain  $\times 100$

### Discussion

Malignant melanoma involving the gastrointestinal tract and other abdominal cavity organs is an uncommon and often occult lesion (Henriques, 1955; Kazman and Zakaukas, 1956; Larmi, 1960; Bäckman and Davidsson, 1965; Gabriele and Jouffre, 1969; Willbanks and Fogelman, 1970; Johansson et al., 1970). Raven (1953) collected from the literature 2,193 cases of primary and secondary malignant melanoma and found the following rates in the gastrointestinal tract: Esophagus 4 cases (0.18%), small intestine 39 (1.77%), biliary tract 13 (0.59%), anorectal region 123 (5.6%). Almost all these lesions are metastatic malignant melanomas to the gastrointestinal tract, though primary malignant melanomas have been found in the esophagus and in the small intestine (Vetner, 1961; Bartsch, 1961; Mikuz et al., 1975). No cases of primary melanoma of the stomach and colon (except the anorectal lesion) have been described (Musher and Lidner, 1974).

If secondary melanomas to the gallbladder are excluded, to date only seven cases of primary melanoma of this organ have been reported (Table 1). The present case and the seven previously reported cases have similarities with each

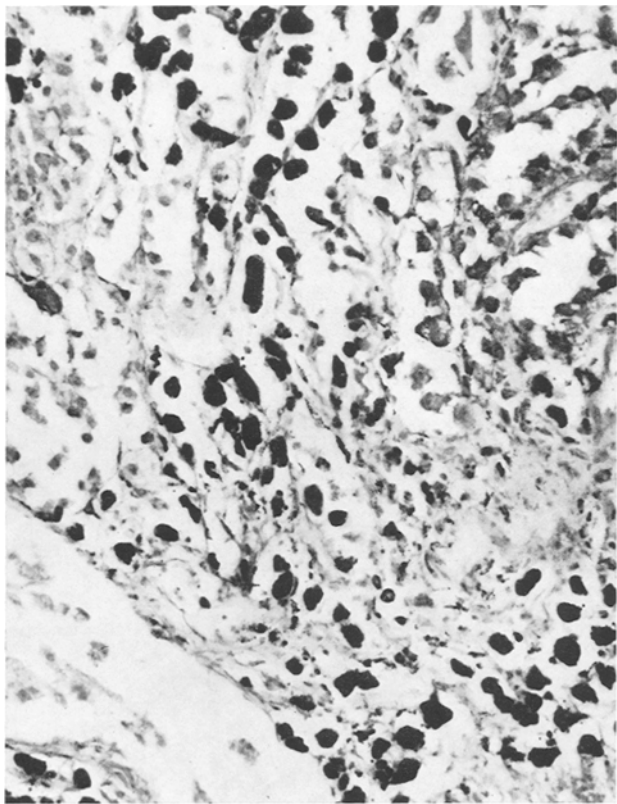


Fig. 3. Scattered throughout the tumor there are numerous clumps of melanin-containing cells. Masson-Hamperl's stain  $\times 160$

Table 1. Details of primary malignant melanoma of the gallbladder

Author	Age and Sex	Pathologic findings	Metastases
Wieting and Hamdi (1907)	40 years; ♀	Polypoid	Omentum, vertebra, meninges, nerve roots, pouch of douglas
Rosenthal (1931)	48 years; ♂	Polypoid	Jejunum, lungs, bronchial lymph node, brain, kidneys
Pauter and Gallavan (1951)	65 years; ♂	Polypoid	Brain
Thayer et al. (1955)	69 years; ♀	Polypoid	Lungs, adrenals, meninges
Walsh (1956)	45 years; ♂	Polypoid	No metastasis
Jones (1961)	72 years; ♂	Polypoid	Spleen, mediastinal lymph node, small bowel
Raffensperger (1963)	46 years; ♀	Polypoid (2)	No metastasis
Sierra-Callejas and Warecka (present case)	44 years; ♂	Polypoid (2)	Hepatohiliar lymph node, adrenal, brain

other, the most striking common features of the tumor in the gallbladder being its size, ranging from 2 to 7.5 cm in length and from 2 to 4 cm in breadth. The second important common feature is its polypous and melanotic structure and that the tumor arises from the gallbladder wall by a fibrous pedicle with septa often containing blood vessels.

In our case, tumors were present in the brain and right adrenal, and the question naturally arises as to whether these were primary. In the brain the lesions consisted of multiple localized nodules of tumor without accompanying melanosis of the meninges which may in rare cases be the origin of primary melanoma. Moreover, a primary meningeal melanoma does not give rise to extracranial metastases (Gibson et al., 1957). The adrenals could be the primary localization of these tumors as in Knisely's report of such a case in 1946, but primary malignant melanoma of this organ is not accepted by several authors (Dietrich and Siegmund, 1926; Roulet, 1974). For this reason we consider that in the case reported by Thayer et al. in 1955, the primary site of the melanoma may have been in the gallbladder.

In the histogenesis of these tumors, the possibility of a heterotopia or a metaplasia being the source of origin has been considered (Walsh, 1956; Jones, 1961). The gallbladder is derived from the entodermal intraembryonic part of the yolk sac—the primitive gut—(Tuchmann-Duplessis and Haegel, 1972), part of which normally develops squamous epithelium in becoming the definitive esophagus. It is possible that a heterotopia might develop in the gallbladder and give rise to a melanoma, but, to date there is no report of heterotopic squamous epithelium in the gallbladder.

Walsh (1956) found "junctional activity" and considers this as a special feature of primary melanoma of the gallbladder. He suggests that they are relatively slow-growing, autochthonous tumors, analogous to the simple papilloma of the gallbladder, and that there is a possibility that the development of an epithelial polyp with squamous metaplasia subsequently gives rise to a malignant melanoma; however, this explanation is only hypothesis. Squamous metaplasia is well known in association with carcinoma, but it has never been described in a benign tumor of the gallbladder (Jones, 1961). In our case and in the remaining six cases there was no squamous epithelial metaplasia present and this theory might be only speculative.

Melanoblasts are normally present in some parts of the body, but we cannot explain the presence of the melanoblasts in the gallbladder; however, if we consider that Masson (1948) says "Since the area of distribution of the elements issued from neural crests is as wide as that of the peripheral nervous system, one may think that neuro-ectodermal melanoblasts may, occasionally, be found anywhere, even in the intestine, and these give rise to primitive melanomas", this could possibly be the origin of the primary malignant melanoma of the gallbladder.

### References

- Bäckman, H., Davidsson, L.: Metastases of malignant melanoma in stomach and small intestine. *Acta med. scand.* **178**, 329–335 (1965)  
Bartsch, W. M.: Primäre maligne Melanome des Ösophagus. *Bruns' Beitr. klin. Chir.* **202**, 427–440 (1961)

- Dietrich, A., Siegmund, H.: Die Nebenniere und das chromaffine System (Paraganglien, Karotisdrüse, Steissdrüse). In: Handbuch der speziellen pathologischen Anatomie und Histologie, Bd. VIII, S. 951–1089. Hrsg.: von Henke und Lubarsch. Berlin: Springer 1926
- Gabriele, R., Jouffre, C.: Un cas de melanome de la vésicule biliaire. *Lyon chir.* **65**, 682–685 (1969)
- Gibson, J. B., Burrows, D., Weir, W. P.: Primary melanoma of the meninges. *J. Path. Bact.* **74**, 419–438 (1957)
- Henriques, C. G.: A case of secondary melanoma of the gallbladder presentin as acute cholecystitis. *Brit. J. Surg.* **42**, 663–665 (1955)
- Johansson, H., Krause, U., Olding, L.: Pancreatic metastases from a malignant melanoma. *Scand. J. Gastroent.* **5**, 573–575 (1970)
- Jones, C. H.: Malignant melanoma of the gallbladder. *J. Path. Bact.* **81**, 423–430 (1961)
- Kazmann, H. A., Zakaukas, C. L.: Malignant melanoma of the gallbladder. *Amer. J. Surg.* **92**, 469–471 (1956)
- Knisely, R. M., Baggenstoss, A. H.: Primary melanoma of the adrenal gland. *Arch. Path.* **42**, 345–349 (1946)
- Larmi, T. K. I.: Malignant melanoma of the gallbladder. Report of a case resulting in an external biliary fistula. *Acta chir. scand.* **119**, 502–505 (1960)
- Lerner, A. B., Fitzpatrick, T. B.: The control of melanogenesis in human pigment cells. In: *Pigment cell growth*, pp. 319–333. Proceedings of the third conference on the biology of normal and atypical pigment cell growth. New York: Academic Press Inc. 1953
- Masson, P.: Pigment cells in man. In: *The biology of melanomas*, pp. 15–51. Spec. publ. New York: N. Y. Acad. Sci. 1948
- Mikuz, G., Scharfetter, H., Bernard, W., Reisegger, W.: Das primäre maligne Melanoblastom des Ösophagus. *Zbl. allg. Path.* **119**, 189–193 (1975)
- Musher, D. R., Lidner, A. E.: Primary melanoma of the esophagus. *Amer. J. dig. Dis.* **19**, 855–859 (1974)
- Pauter, E. E., Gallavan, E. M.: Melanoma of the brain and gallbladder. *Arch. Path.* **51**, 238–245 (1951)
- Raffensperger, E. C., Brason, F. W., Triano, G.: Primary melanoma of the gallbladder. *Amer. J. dig. Dis.* **8**, 356–363 (1963)
- Raven, R. W.: Problems concerning melanoma in man. In: *Pigment cell growth*, pp. 121–137. Proceedings of the third conference on the biology of normal and atypical pigment cell growth. New York, N. Y.: Academic Press Inc. 1953
- Rosenthal, S. R.: Primary melanocarcinoma of the gallbladder. *Amer. J. Cancer* **15**, 2288–2300 (1931)
- Roulet, F. C.: Nebenniere. In: *Histologische Geschwulstdiagnostik*, S. 380–386, Hrsg.: A. von Albertini. 2. Aufl. Stuttgart: Thieme 1974
- Thayer, K. H., Williams, O. O., Rowe, D.: Malignant melanoma of the gallbladder. Report of a case and review of the literature. *Ariz. Med.* **12**, 15–18 (1955)
- Tuchmann-Duplessis, H., Haegel, P.: Organogenesis. In: *Illustrated human embryology*. Vol. II, pp. 22–43. New York: Springer and London: Capmann & Hall, Paris: Masson & Cie. 1972
- Vetner, M. O.: Primaert malignant melanom i tyndtarmen. *Nord. Med.* **66**, 1035–1037 (1961)
- Walsh, T. S., Jr.: Primary melanoma of the gallbladder with cervical metastases and fourteen and half year survival. First histologically proved case. *Cancer (Philad.)* **9**, 518–522 (1956)
- Wieting, Hamdi: Über die physiologische und pathologische Melaninpigmentierung und den epithelialen Ursprung der Melanoblastome. Ein primäres Melanoblastom der Gallenblase. *Beitr. path. Anat.* **42**, 23–84 (1907)
- Willbanks, O. L., Fogelman, M. J.: Gastrointestinal melanosarcoma. *Amer. J. Surg.* **120**, 602–606 (1970)

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