

## 統合失調症患者の病理解剖の意義

### － 転移性肝癌で死亡した統合失調症の一剖検例を通して －

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## The aims of autopsies for patients with schizophrenia

### － Autopsy findings in a case of schizophrenia dying of metastatic liver cancer －

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## 要旨

60歳代男性の統合失調症の一剖検例を報告した。転移性肝癌が発見され、その2ヵ月後には肺や胸膜への転移による呼吸不全で死亡した。死後1時間で脳および身体臓器一般について剖検が行われ、脳では統合失調症で矛盾しないかの確認のほか、血管性病変の合併の程度や癌転移の有無を知るために、一般身体的には転移性肝癌の原発巣の検索および癌転移臓器の範囲を知る目的で剖検が行われた。さらに、右半脳は冠状断の後、ドライアイスで速やかに凍結の後、 $-80^{\circ}\text{C}$  に保存され、国立精神・神経センター神経研究所と国立病院機構によるブレインバンク(Research Resource Network: RRN) に登録された。こうして、世界中の研究者によって、厳重な倫理審査のもとに統合失調症研究に使用され、本症の原因解明、治療法開発に貢献することが期待される。

本例は、高校卒業後頃から、難治性の妄想、幻覚、易怒性、衝動行為、母親への暴力行為の頻発にて精神科に入退院を繰り返し、10年ほど前からは病院で隔離の状態であった。3年前に、急に全身の脱力発作を来たして脳梗塞の合併と診断された。2ヵ月前、胸部単純X線写真の異常陰影の発見を契機に、胸膜、肋骨、脊椎骨、骨盤、肝臓に癌が見つかり、原発巣不明のまま、呼吸不全で死亡した。

一般身体的には、腺癌細胞の浸潤・増殖巣が、肝臓、膵臓、両側肺・胸膜、骨(肋骨、胸骨、椎骨、腸骨)、両側副腎、甲状腺にみられた。肺には、肺炎とびまん性肺胞障害、および腺癌の散在性小転移巣が多数認められ、これらが呼吸不全を来たした原因と考えられた。腺癌細胞の免疫染色では、cytokeratin 19と20が陽性、cytokeratin 7が陰性であった。消化管全体に触診上腫瘍性病変は明らかでなかったが、この免疫染色所見は大腸など消化管起源の腺癌を最も強く疑わせるものであった。膵臓や胆管、前立腺の腺癌でもあり得るが、prostate-specific antigen (PSA) は陰性であった。固定前脳重量は

1,150 g で、大脳皮質（前頭葉、帯状回など）や海馬アンモン角、嗅内野では、神経細胞の配列異常があるような印象があるが、異常所見か否かは判断に苦慮する所見と思われた。しかしながら、海馬アンモン角での錐体細胞の disorientation index (Kuroki and Matsushita)は、それほど高値ではなかった。病理所見は統合失調症として矛盾しないものであったが、中脳黒質には神経細胞脱落や遊離メラニン、アストロサイトーシスが認められたが、統合失調症との関係は不明である。ほか、尾状核や大脳白質、視床には新旧の梗塞性病変が認められた。鳥取臨床科学 3(1), 91-114, 2010

## Abstract

An autopsy of a 60-year-old man with a history of schizophrenia for approximately 45 years was reported. Two months before he finally died of respiratory failure due to cancer metastasis to the lung and pleural, multiple liver cancers that were thought to be metastatic from an unknown primary lesion were found. The brain and body organs were autopsied 1 hour after death. In order to confirm whether the brain showed autopsy findings consistent with schizophrenia, vascular ischemic changes and small cancer metastatic lesions, and to determine which organs the cancer had metastasized to and originated from. The right half of the brain was cut coronally, immediately frozen, stored at -80°C, and enrolled in the brain bank “Research Resource Network (RRN)” run by the National Center of Neurology and Psychiatry (NCNP) and the National Hospital Organization (NHO) in Japan. This stored brain is expected to be used by schizophrenia researchers worldwide under strict review by the ethical committee. Such research is expected to participate in clarification of the etiology and development of the therapies.

This patient had repeated admissions and discharges from psychiatric hospitals because of intractable delusion, hallucination, irritability, impulsive behaviors, and frequent violence against his mother, which began to be manifest after he graduated from high school. He began to be admitted to the isolation ward 10 years before his death. Three years before his death, he suddenly exhibited generalized weakness and was diagnosed as having cerebral infarction. Two months before his death, a plain X-ray image depicting an abnormal shadow in the left apical or upper lung field indicated multiple cancers in the left pleura and ribs, vertebral bones, pelvis and liver, but the origin of the cancer had not yet been determined when he died of respiratory failure.

On histological examination of his organs, adenocarcinoma lesions were detected in the liver, pancreas, bilateral lungs and pluera, bones (the ribs, sternum, vertebrae, and ilium), bilateral adrenal glands, and thyroid gland. In addition, microscopic observation of the lungs demonstrated pneumonia, diffuse alveolar damage, and dissemination of multiple small adenocarcinoma lesions, which were thought to have caused respiratory failure. On immunohistochemistry, adenocarcinoma cells were positive for cytokeratins 19 and 20, but negative for cytokeratin 7, strongly suggesting that the carcinoma cells had originated from the digestive tract, specifically from the colon, although, no tumor lesions were macroscopically found in the digestive tract. However, possibilities that the metastases had been derived from the pancreas, cholangioduct, and prostate could not be excluded, although the cells were negative for prostate-specific antigen (PSA). The brain weighed 1,150 grams before fixation. Microscopic examination of pyramidal neurons in the cerebral cortices (frontal and cingulate), Ammon’s horn of the hippocampus, and entorhinal cortex suggested disorientation of these neurons; however, it is very difficult to determine that such disorientation is abnormal or specifically related to the pathological mechanisms in schizophrenia. As one of the methods of identifying such neuronal disorientation, Kuroki and Matsushita reported that a disorientation index can be used. The disorientation indices of the hippocampus in the present case were not as high as that previously reported in tissue sections from schizophrenia brains. On immunohistochemistry for tau, amyloid  $\beta$ -peptide,  $\alpha$ -synuclein and TDP-43, the possibilities of known neurodegenerative disorders such as Alzheimer and Parkinson diseases were all excluded; therefore, the neuropathological findings in the present case were consistent with schizophrenia, except for two findings: neuronal loss, free melanin and astrocytosis in the substantia nigra, and fresh and old ischemic lesions in the cerebral white matter, caudate and thalamus. It remains to be determined whether the nigral lesions are related to schizophrenia. *Tottori J. Clin. Res.* 3(1), 91-114, 2010

Key Words: 統合失調症, ブレインバンク, 死後脳研究, disorientation index, cytokeratin, 中脳黒質, 転移性肝癌・肺癌; schizophrenia, brain bank, postmortem brain research, disorientation index, cytokeratin, substantia nigra, metastatic liver and lung cancers

## 1. はじめに

60 歳代男性の統合失調症の剖検の機会を得