A 68-year-old male presented with an abnormality on upper gastrointestinal endoscopy during a health check. He was diagnosed with malignant melanoma of the esophagus using biopsy tissue and admitted for surgery. Thoracoabdominal computed tomography did not reveal any tumor lesions in the esophagus wall. Swelling of the lymph node and metastases were not found in other organs. The preoperative diagnosis was T1N0M0 and stage I disease, and an operation was performed. The patient was diagnosed with T1a-LPM, N0M0, stage 0 according to the Japanese Classification of Esophageal Cancer. Melanosis was diagnosed in gross appearance in the black mucous membrane part without the upheaval.

Nine months have elapsed since surgery, and the patient has survived without recurrence. Esophageal malignant melanoma is a relatively rare disease, and there are no treatment guidelines. We report our experience with a case of resection of esophageal malignant melanoma.

Key words: esophageal malignant melanoma, melanosis, esophageal melanosis

Introduction

In Japan, squamous cell carcinoma is the most common malignant tumor of the esophagus, and incidence of malignant melanomas is approximately 0.1–0.2% in esophageal cancer.\(^1\)\(^-\)\(^2\)

Esophageal malignant melanoma has a poor prognosis, with a mean survival time of 9.8 months after the start of therapy. Currently, there are no treatment guidelines for this disease.\(^3\)-\(^5\).

The association between esophageal malignant melanoma and esophageal melanosis is controversial, and there is no clear evidence that the latter is a former outrider lesion. In addition, malignant melanoma is the disease that may utter to a whole body, and biopsies have a risk of inducing dissemination when performed for primary cutaneous lesions. For melanosis, it is necessary to examine adaptation of the biopsy in the malignant melanoma of the gastrointestinal tract primary. To diagnose malignant melanoma, endoscopy is the preferred method.

Malignant melanoma may appear throughout the whole body primary and greatly influence treatment and convalescence when an esophageal lesion is one from head to foot of the metastasis.\(^6\)-\(^8\)

Therefore, it is important to determine metastatic characteristics in the esophageal malignant melanoma if it is primary. Here, we report a case of esophageal malignant melanoma.

Case report

A 68-year-old male presented with an abnormality on upper gastrointestinal endoscopy during a
health check. There were black bands found in the mucosa of the thoracic esophagus located 30 cm, 33 cm, and 37 cm from the incisors. He was diagnosed with malignant melanoma of the esophagus using biopsy tissue and admitted for surgery.

The patient had a previous history of diabetes, which was being under oral treatment. There were no abnormal findings in the blood examination. His hemoglobin A1c level was 6.4%. The tumor markers carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), squamous cell carcinoma (SCC), and cytokeratin 19 fragment (CYFRA) were all in the normal range, and 5-S-cysteinyldopa also measured at a normal level of 4.4 nmol/l.

The upper gastrointestinal endoscopy revealed black mucosa and a surface protrusion with a height 2/5 of the circumference in the thoracic esophagus located 33 cm from the incisors (Figure-1A). Black mucosa was also seen in places without protrusions located 30 cm and 37 cm from the incisors (Figure-1A, B).

The surface protrusions were located mainly on the basal stratified squamous epithelium, with hyperplasia of polygonal and spindle cells containing melanin granules. The cells contained swollen nuclei and pronounced nucleoli. These cells were positive for S-100, and therefore the patient was diagnosed with malignant melanoma. A biopsy of the black mucosa without accompanying protrusions revealed melanosis, with no finding of malignancy.

By thoracicoabdominal CT examination, no tumor lesions were identified in the esophagus wall, and swelling of the lymph node and metastases in other organs were not found.

We completely removed the thoracic esophagus by thoracolaparotomy on the right side, with dissection of two regional lymph nodes and cervical esophagogastric anastomosis.

A spotted region with accompanying black pigmentation, an irregular shape, and an unclear boundary was found in the middle of the thoracic esophagus. The tumor measured 15×20 mm in diameter. Melanosis was scattered throughout the entire esophagus. The boundaries of the tumor and melanosis were unclear, and to the gross appearance, they were continuous (Figure-2).

Histopathologically, the resected tumor was T1a-LPM, N0, M0, ly0, v0, PM(-), DM(-), and stage 0 according to the Japanese Classification of Esophageal Cancer. In the surface protrusions, there was proliferation of irregularly sized and abnormally shaped cells with enlarged nuclei, and cells with
brown melanin granules densely infiltrated from the basal layer of the squamous epithelium to the proper mucosa (junctional activity) (Figure-3A). Therefore, the diagnosis of malignant melanoma was confirmed. Vascular invasion was not found. The tumor cells formed irregular alveoli, and the basal membrane of the squamous epithelium was unclear. The nuclei of the infiltrating cells were large and irregular (Figure-3B). Additionally, the infiltrating cells were positive for S100 protein (Figure-3C).

Gross appearance of histological images of the black mucosa without accompanying protrusions found clear cells with abnormal shapes and melanin granules in the basal stratified squamous epithelium. There were many cells that contained relatively weak nuclear abnormalities, including some that were deeply pigmented and had irregular shapes. In the peripheral region, the cells had weaker abnormalities. Therefore, this was diagnosed as melanosis. We found histiocytes that strongly absorbed melanin pigment in the subepithelial interstitial tissue, but we did not find tumor infiltration (Figure-4). In this case we also did not find any lymph node metastasis.

After surgery, the patient developed mild hoarseness and underwent rehabilitation. The patient gradually recovered and was discharged on day 28. Fifteen months have elapsed since surgery, and the patient has survived without recurrence.

Discussion

Malignant melanoma is derived from cells that produce melanin, and it is a disease that can metastasize early. In 50% to 80% of cases, the primary lesion is a skin lesion, and the frequency of primary lesions in the digestive tract is low. However, among malignant melanomas of the digestive tract, whether in Japan or elsewhere, there have been many reported cases for which the esophagus, rectum, or anorectal junction is the primary site, and among these, 30% of the reported cases occur in the esophagus.\(^1\)\(^2\)

Primary malignant esophageal melanomas comprise 0.1% to 0.2% of all malignant esophageal tumors, with an average age at onset of 60.4 years, which is less than that of esophageal cancer, and malignant esophageal melanoma is also more common in males, by a factor of 2 to 1.\(^3\)-\(^6\) The middle and lower esophagus are the most common sites, with 76.2% of cancer occurrence, and at the time of diagnosis, the proportion of cases of tumors less than 2 cm in diameter is an extremely low 8.3%. Therefore, in most cases, the tumor diameter is more than 2 cm when first discovered. Reportedly, 79.2% of cases present with surface protrusions or tumefacient protruding conditions by gross inspection. Histopathologically, cells have abnormal

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**Figure-3**

A. Hematoxylin and eosin (HE) staining (×200) of black mucosa accompanying surface protrusion at 33 cm from the incisors. B. HE staining after bleaching with the potassium permanganate oxalic acid method (×400) of black mucosa accompanying surface protrusion at 33 cm from the incisors. C. Immunostaining after the potassium permanganate oxalic acid method (×400) of black mucosa accompanying surface protrusion at 33 cm from the incisors.

**Figure-4**

Hematoxylin and eosin (HE) staining (×200) of black mucosa at 30 cm from the incisors.
shapes, ranging from multiple ridges to spindle shapes, with melanin granules in the cytoplasm, and many cells exhibit medullary proliferation with prominent nucleoli.

The frequency of esophageal melanosis, which is noted by pigmentation uptake in the esophagus, is 0.11% in individuals in good health. This condition describes benign melanocyte proliferation in the basal esophageal mucosa. Nakamura et al. reported that 20 cases out of 67 cases (29.9%) of malignant esophageal melanoma are accompanied by esophageal melanosis, and a relationship between malignant esophageal melanoma and esophageal melanosis is strongly suspected. However, there have only been two reported cases in which esophageal melanosis became malignant as it was being monitored, and at the present time, there is no clear basis for viewing esophageal melanosis as a precursor lesion for malignant esophageal melanoma.

Opinions differ as to whether or not melanosis is a precursor lesion for malignant melanoma, according to the primary organ site. With regard to skin, in approximately 75% of cases, melanoma occurs in normal skin with no precursor lesion, and for the other cases it accompanies a preexisting melanocytic nevus. However, although a relationship is suspected between malignant melanoma and melanosis in the esophagus and oral cavity mucosa, no reports strongly suggest a precursor lesion that could be called a "melanoma within melanosis." In the present case, the boundary between partial melanoma and melanosis was unclear to the gross appearance, but there was no finding of "melanoma within melanosis".

To distinguish esophageal melanosis from malignant esophageal melanoma, junctional activity, which refers to increased cell abnormalities in the basal esophageal mucosa, the randomness of cell arrangement, and discontinuity of the basal membrane of the esophageal epithelium, is a very important histological finding. Malignant melanoma stains positively for HMB-45, S-100 protein, and neuron-specific enolase, but this is merely an aid to diagnosis. At the present time, a decisive diagnosis can only be performed based on histopathological findings. Preoperative biopsies are reportedly performed for approximately 65% of cases, and the rate of correct diagnosis is approximately 80%, which is not especially high. Biopsy of the lesion is contraindicated for primary malignant skin melanomas, and the same strategy is often followed for esophageal lesions. Therefore, some facilities perform surgical procedures without a biopsy in order to avoid the risk of dissemination. However, a significant difference in the five-year survival rate was not found based on biopsy performance, and thus there is no data to establish a relationship between biopsy and dissemination. Therefore, for flat lesions, as in this case, minimal biopsies are thought to be appropriate to determine the treatment plan.

Malignant melanoma can occur anywhere in the body, and if an esophageal lesion is a systemic metastasis then that greatly influences the treatment method and prognosis. Therefore, for malignant esophageal melanoma it is important to distinguish whether or not it is primary or metastatic, and junctional activity is an important diagnostic factor for diagnosing primary malignant esophageal melanoma, according to Allen et al. In the present case, we found melanin-containing tumor cells in the epithelium, and we verified their existence with images of subepithelial infiltration (junctional activity), thereby satisfying the diagnostic requirement for primary esophageal melanoma.

Since the effectiveness of chemotherapy and radiation therapy is low, surgical removal is the usual treatment method. However, even in surgical cases, the prognosis is poor, with a five-year survival rate of 4.2%. For category II and III cases, according to the International Union Against Cancer (UICC) classification, postoperative auxiliary chemotherapy is performed with DAVFeron (Dacarbazine (DTIC), Nimustine (ACNU), vincristine (VCR), and Interferon-β (INF-β) local administration). In cases for which recurrence or metastasis has been found, chemotherapy is appropriate, and only DTIC is administered. However, the effectiveness is only approximately 20%.

On the other hand, a new medicine began to come up one after another from 2011, and the treatment of the melanoma is changing.

But the one year survival rate with the cytotoxic agent (Dacarbazine, etc.) was 35% and the two years survival rate was 10 several percent, the two survival rate with the new medicine reaches 80% in the latest clinical trial. The new medicine consists of
an immune checkpoint inhibitors and molecular target therapeutic agents\textsuperscript{22–25}.

The combination of immunological methods, such as dendritic cell– and oncolytic virotherapy, may show higher therapeutic effects\textsuperscript{22}.

Looking at the international data, most primary malignant melanoma of the esophagus cases are advanced. Of the 85 cases reported in the 10 year period from 2005 to 2014 in the PubMed database, superficial tumors, lesions limited to the submucosal layer, totaled 9 cases (10.6%). Only 6 cases (0.5%) of early stage mucosal primary malignant melanoma of the esophagus (PMME) were seen in the PubMed database in the past 10 years.

Considering patient invasion, a treatment of mucosal PMME would be best to perform endoscopic resection. But this would be limited to one or two lesions and in cases of multiple origins just melanocytosis\textsuperscript{24}.

The present case was multiple origins and extensive melanocytosis.

However even with biopsy it can be difficult to obtain a correct diagnosis of mucosal malignant melanoma. There was an extremely rare case of mucosal PMME with proper mucosal layer invasion, in which systemic metastasis occurred rapidly after resection resulting in death\textsuperscript{26, 27}. This indicates the difficulty in the pathologic diagnosis of PMME also on resected specimens.

There is also a report of an extensive lesion (pT1a–LPMN0) in which a patient die of liver and lung multiple metastasis at 19 months after radical surgery\textsuperscript{28}. It indicates we should treat it carefully.

The present case, in which an early–stage malignant esophageal melanoma lesion was diagnosed via preoperative diagnosis, and extensive melanosis was also observed, the existence of multiple lesions may be suspected, and selection for endoscopic surgery may be difficult. Naturally, the first choice for standard treatment is radical surgery.

With recent developments in diagnostic techniques and therapeutic methods, the number of early stage lesions is increasing. In addition to this, to developments in endoscopic surgery\textsuperscript{29, 30}, molecular targeting agents and immune checkpoint inhibitors will reduce a menace of malignant melanoma.

Conflict of interest

The authors declare no conflict of interest associated with this manuscript.

References


