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【 CASE REPORT 】

Spontaneous Regression of Epithelioid Angiosarcoma in a Young Woman

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Abstract:
A 20-year-old Japanese woman with a history of pulmonary atresia was referred to our hospital after the detection of an abnormal mass in the right lung and mediastinal lymphadenopathy. A cytological specimen obtained by transbronchial brushing indicated that the pathological diagnosis was non-small cell lung cancer. During the follow-up period, the tumor spontaneously regressed. At four months after the diagnosis, she experienced sudden bleeding from the small intestine. The histological characteristics of the small intestine tumor were compatible with the cytological characteristics of the lung tumor. Detailed immunohistochemical analyses led to a final diagnosis of epithelial angiosarcoma of the small intestine, which might have formed metastatic lesions in the lung.

Key words: epithelioid angiosarcoma, spontaneous regression, small intestine and lung, young woman, radiation exposure

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Introduction

The spontaneous regression (SR) of malignant disease is rare. SR is recognized as the complete or partial disappearance of a disease continuing for at least 1 month in the absence of effective anticancer treatment (1). More than half of these rare cases involve carcinoma of the kidney, neuroblastoma, malignant melanoma, or choriocarcinoma. The SR of angiosarcoma is considered to be a particularly rare event. We herein report a case of the SR of epithelioid angiosarcoma of the small intestine in a young woman.

Case Report

A 20-year-old Japanese woman presented to a nearby hospital with cough and right back pain, and was diagnosed with pneumonia. She had no hemoptysis, hemosputum or rusty sputum. Despite treatment with antibiotics, her symptoms did not improve and she was referred to our hospital for further investigation.

She had a history of congenital pulmonary atresia and had undergone surgery 4 times. She had no history of smoking. Her mother had been successfully treated for malignant lymphoma. Her laboratory data indicated mildly elevated levels of C-reactive protein (9.09 mg/dL), white blood cells (9,500/μL), neutrophils (83.4%) and slight anemia (hemoglobin 9.1 g/dL), but no specific elevations in tumor markers for lung cancer or malignant lymphoma (interleukin 2-receptor 83.3 U/mL) or auto-antibodies such as rheumatoid factor (<10.0 IU/mL) or anti-neutrophil cytoplasmic antibodies (<1.0 EU). Blood tests and culturing performed in the previous hospital showed no signs of infection: procalcitonin-negative, β-D-glucan-negative, cryptococcal antigen-negative, Aspergillus antigen-negative, sputum bacterial, acid-fast bacterial and fungus culture-negative, and blood culture-negative. Computed tomography (CT) showed a mass in the right lower lobe of the lung measuring 5.0×4.0 cm with multiple nodules in the bilateral lungs and multiple mediastinal lymphadenopathies (Fig. 1a and b). A bronchoscopic examination

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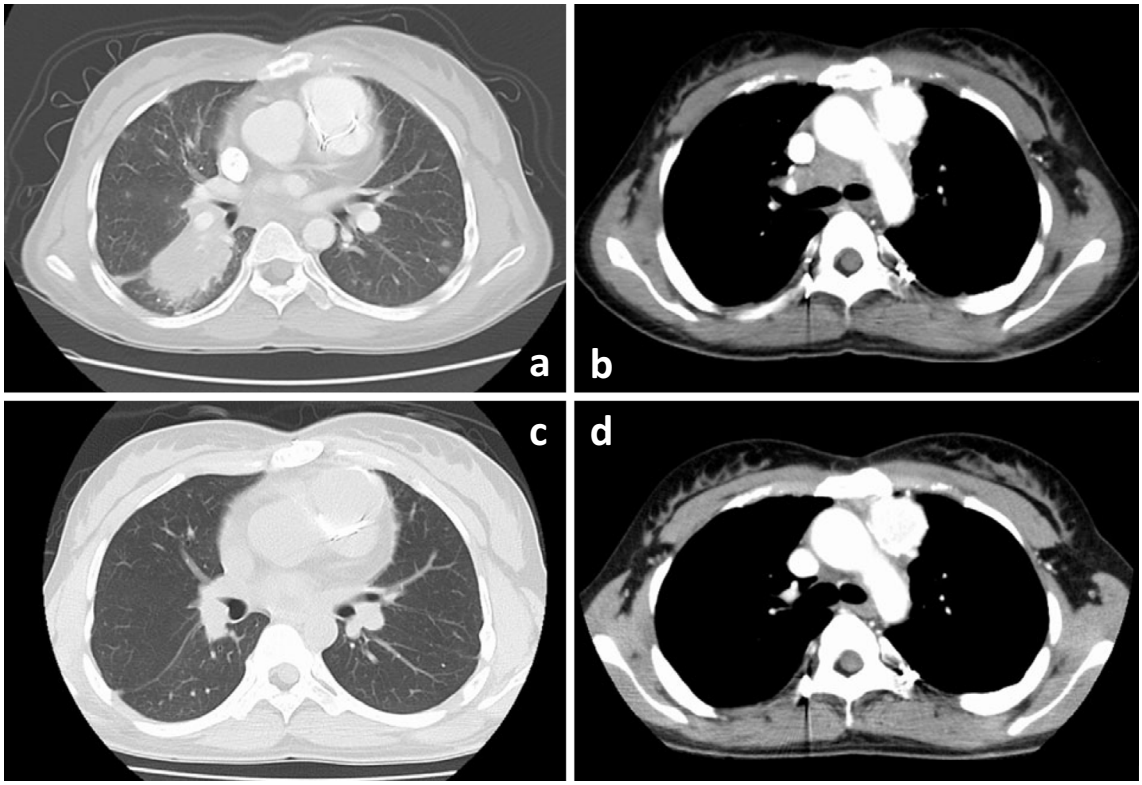

Figure 1. **Chest computed tomography (CT). (a, b) CT on the first visit, showing a right lower lobe mass, multiple nodules in both lungs, and multiple mediastinal lymphadenopathies. (c, d) Chest CT at 2 months after diagnosis, showing SR of the tumor and lymphadenopathies. SR: spontaneous regression**

showed almost complete occlusion of the right B^6b-c with a partially necrotic tumor and an edematous mucosa with reddening in the right secondary carina and right upper- and lower-lobe bronchi (Fig. 2a). A small specimen obtained from the peripheral lesion from a small passage through the right B^6b-c on transbronchial biopsy under endobronchial ultrasonographic guidance showed normal tissue. A cytological study of a specimen obtained from the same peripheral lesion by brushing revealed non-small cell carcinoma with enlarged nuclei, irregular nuclear form, and conspicuous nucleoli (Fig. 2b). The histopathological examination of a cell block preparation (Hematoxylin and Eosin staining) showed atypical cells with giant bizarre nuclei and eosinophilic bodies with inflammatory cells in the background (Fig. 2c). An immunohistopathological study of cell block preparations showed that the tumor cells were pancytokeratin-positive, leukocyte common antigen (LCA)-negative, thyroid transcription factor-1 (TTF-1)-negative (Fig. 2d), anaplastic lymphoma kinase (ALK)-negative, cytokeratin (CK)7-positive (Fig. 2e), CK20-negative, and anti-p40 antibody-negative. No epidermal growth factor receptor (EGFR) gene mutations were identified. The pathological diagnosis was non-small cell lung carcinoma (NSCLC), and the clinical diagnosis was NSCLC, cT2bN2M1a, stageIV.

Two weeks after reaching this diagnosis, ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT detected the uptake of FDG in the right lower lobe alone [maximum standard uptake value (SUV), 3.9], not in the enlarged mediastinal lymph nodes. The same scan revealed that size of the tumor in the right lung, the nodules in both lungs, and the multiple mediastinal lymphadenopathies had decreased in comparison to the previous CT scan. No other distal metastases were apparent on PET/CT or brain magnetic resonance imaging. Two months after the diagnosis, the tumor was observed to have undergone further SR on chest CT. We therefore decided to monitor the status of this lung tumor without therapy.

At four months after the diagnosis, the patient experienced sudden severe melena. Abdominal CT (Fig. 3a) and small-bowel endoscopy revealed that the small intestine was the source of bleeding (Fig. 3b), and emergent abdominal surgery was performed.

Partial resection of the small intestine revealed multiple submucosal tumorous lesions with ulcers and ruptured blood vessels (Fig. 3c). The tumor, which showed no visible bleeding, was left without resection. Microscopically, tumor cells with irregular nuclei and prominent nucleoli were arranged in solid nests and cords (Fig. 4a and b), forming irregular sinusoid-like spaces, against a background of infiltrating inflammatory cells. An immunohistopathological study showed that tumor cells were CK7-positive (Fig. 4c), CK20-negative (Fig. 4d), TTF-1-negative (Fig. 4e), CK19-

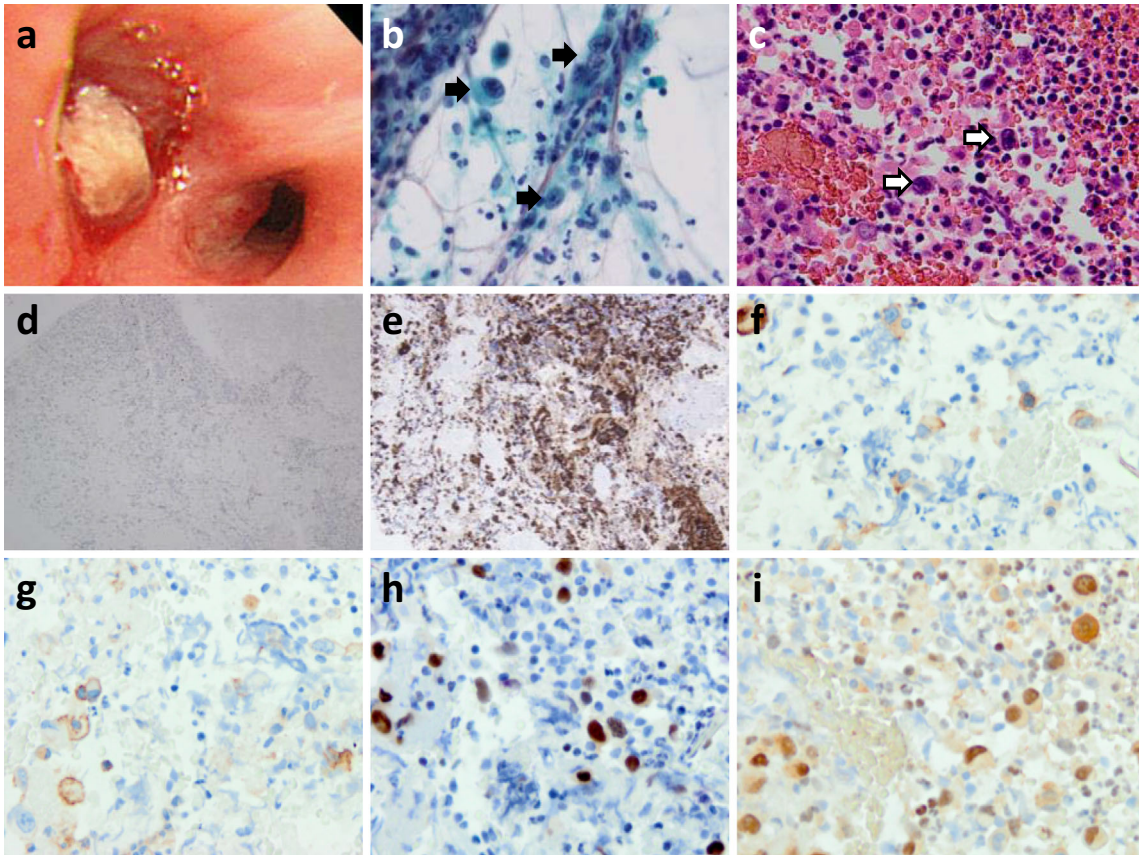

Figure 2. **The bronchoscopic findings. (a) A bronchoscopic examination revealed occlusion of the right B^{6}b-c with a partly necrotic tumor and an edematous mucosa. (b) The cytological study of a specimen obtained from brushing of the distal lesion obtained at the small passage in the entrance of right B^{6}b-c revealed non-small cell carcinoma with enlarged nuclei, an irregular nuclear form, and conspicuous nucleoli. (c) The histopathological examination of a cell block preparation (Hematoxylin and Eosin staining) showed atypical cells with giant bizarre nuclei and inflammatory cells in the background, ×40. (d-f) An immunohistological analysis showed the following results: TTF-1-negative (d), CK7-positive (e), CD31-positive (f), thrombomodulin-positive (g), ERG-positive (h), and FLI-1-positive (i). TTF: thyroid transcription factor, CK: cytokeratin, ERG: ETS-related gene, FLI: friend leukemia integration**

positive (Fig. 4f), napsin A-negative, CDX2-negative, S100-negative (Fig. 4g), PAX8-negative (Fig. 4h), CD3-positive (Fig. 4i), cancer antigen (CA)125-negative, anti p40 antibody-negative, and α-smooth muscle antigen (SMA)-negative. The infiltrating inflammatory cells were CD4-positive, CD8-positive, granzyme-positive, and perforin-positive. The pathological diagnosis was poorly differentiated carcinoma of the small intestine. These histological characteristics were considered compatible with the cytological characteristics of the primary lung tumor.

Delayed imaging PET/CT at 1 month postoperatively detected the uptake of FDG in the small intestine (Fig. 3d). We decided to start chemotherapy and to treat the patient for advanced lung carcinoma with metastasis to the small intestine, even though the tumor in the lung had almost disappeared. The patient received 4 cycles of chemotherapy with a combination of carboplatin and paclitaxel and did not experience any serious adverse effects. At three months after the final chemotherapy treatment, the uptake of FDG was not apparent on PET/CT. The patient remains alive without any signs of recurrence at 2 years after the completion of chemotherapy.

After this clinical course, we continued to review the case from the perspective of immunohistology (Fig. 5). Additional immunostaining of the specimen from the small intestine revealed that the tumor cells were CK CAM 5.2-positive (Fig. 5b), CD31-positive (Fig. 5c), CD34-negative (Fig. 5d), factor VIII-negative (Fig. 5e), thrombomodulin-positive (Fig. 5f), ETS-related gene (ERG)-positive (Fig. 5g), Friend leukemia integration 1 transcription factor (FLI-1)-positive (Fig. 5h), and podoplanin-negative (Fig. 5i). In the same way, immunostaining of lung cell block preparations revealed that the tumor was CD31-positive (Fig. 2f), thrombomodulin-positive (Fig. 2g), ERG-positive (Fig. 2h) and FLI-1-positive (Fig. 2i). Taken together, we finally decided that the present case should be considered to be epithelioid angiosarcoma of the small intestine that was first detected as lung metastasis.

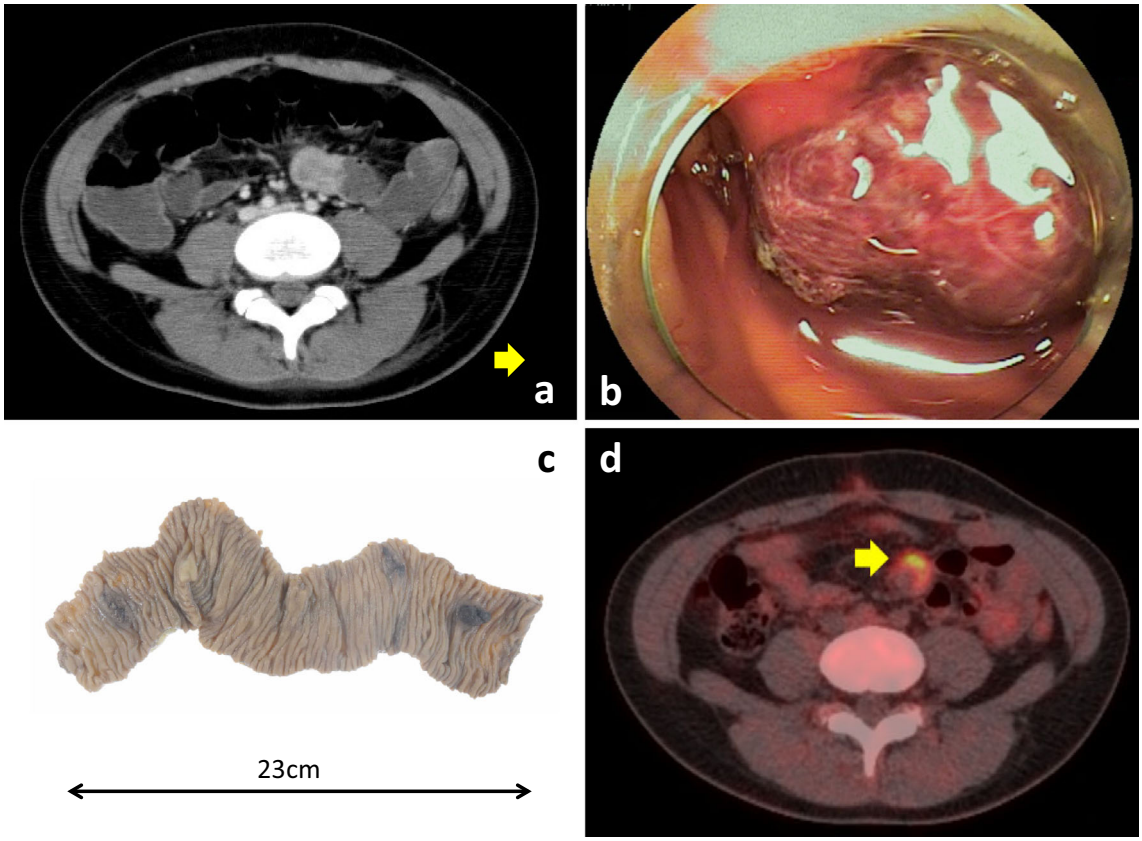

Figure 3. **(a) Abdominal CT during an episode of melena showed a partially high density area in the small intestine. (b) The small-bowel endoscopic findings showed a tumor with distended vessels and bleeding. (c) The partially resected small intestine showed multiple blackish lesions with ulcer formation. (d) Delayed imaging PET/CT (obtained postoperatively) shows the uptake of FDG in the small intestine. FDG: ^{18}F-fluorodeoxyglucose**

Discussion

Angiosarcoma is a rare soft-tissue neoplasm that accounts for 1-2% of all sarcomas, and which occurs most commonly in the skin and subcutaneous tissues. Angiosarcoma arising in the gastrointestinal tract or lung is very rare (2-4). The treatment modalities include surgical resection of the primary tumor and radiotherapy. Some evidence suggests that paclitaxel-based chemotherapeutic regimens may improve survival (5). Epithelioid angiosarcoma is a subtype of angiosarcoma containing large, mildly-to-moderately pleomorphic, round-to-polygonal epithelioid cells that are positively stained for epithelial and endothelial markers, including factor VIII, CD31, CD34, ERG, and FLI-1. Histologically, these tumors are very difficult to distinguish from carcinoma (6). Within 2-3 years of the diagnosis, >50% of patients are dead from disease, but 20-30% of patients are disease-free (6).

The SR of malignant disease was first reported by Everson and Cole (1). The SR of angiosarcoma is a particularly rare event; there is a previous report of the SR of pulmonary metastasis from breast angiosarcoma (7). Several mechanisms are suggested to be involved in the SR of malignant disease, but none have been confirmed. Among the major mechanisms, the activation of immunological systems, which occurs as a result of inflammation, surgery, biopsy, or traumatic injury, may play an important role in SR (8-11). We hypothesized that in our case, the existing inflammatory and immunological background of the pulmonary lesion was further stimulated through the local activation of the immunological systems by the transbronchial biopsy. The activation of the immunological system in tumors of the small intestine might also be increased by surgical stress. The fact that CD4- and CD8-positive T cells were found in preparations of the small intestine may indicate immunological activation. The synergic effects of this inflammatory milieu around the lesion, immunological activation and subsequent chemotherapy may have played an important role in the absence of recurrence during the 2 years of follow-up.

Two controversial issues warrant consideration in our case. First, it is not clear whether we can definitively state that all of the multiple lung nodules represented lung metastasis or whether all of the enlarged mediastinal lymph nodes represented lymph metastasis. Some of the lung nodules might have represented inflammation or infarction of the tu-

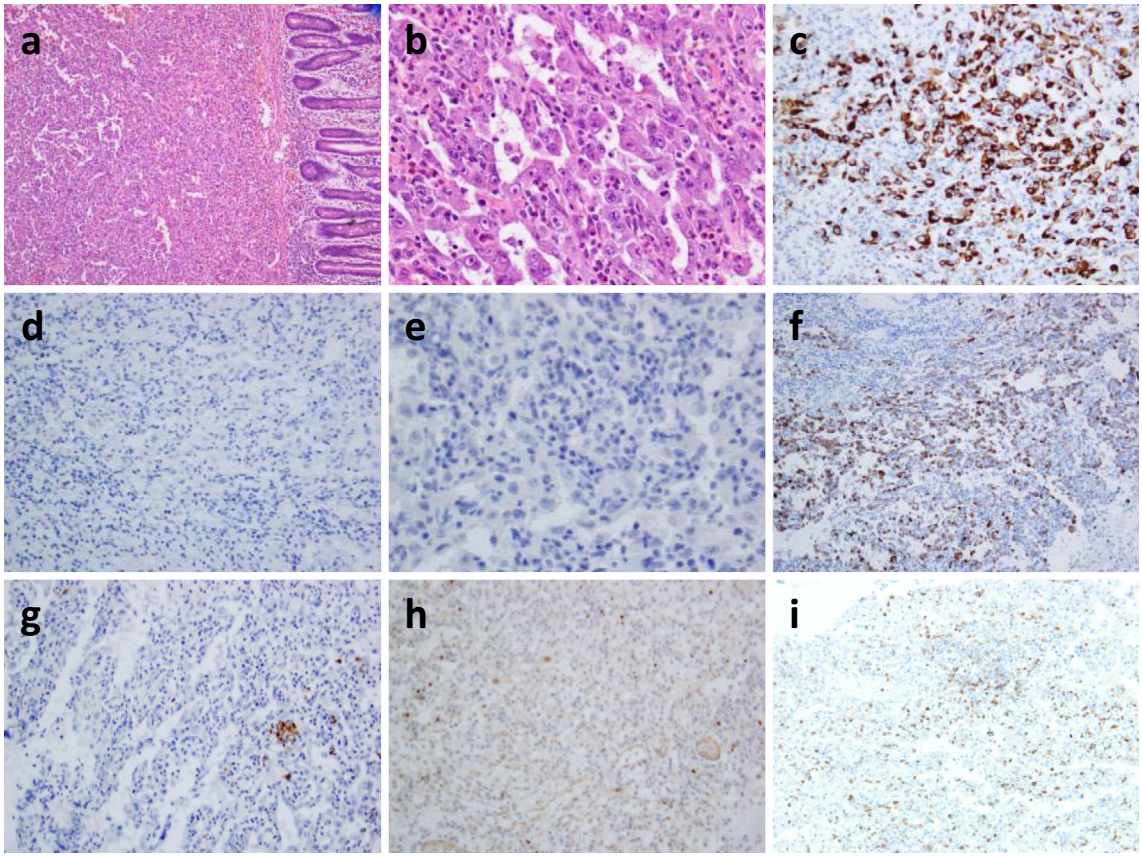

Figure 4. **A surgical specimen of the small intestine. (a, b) The observation of the Hematoxylin and Eosin staining specimen under low-power (a) and high-power (b) views, revealed tumor cells arranged in solid nested and cord-like patterns. (c-i) An immunohistological analysis showed the following findings: CK7-positive (c), CK20-negative (d), TTF-1-negative (e), CK19-positive (f), S100-negative (g), PAX8-negative (h), and the infiltrating lymphocytes were CD3-positive (i). CK: cytokeratin, TTF: thyroid transcription factor**

mor, while the mediastinal lymphadenopathies could have been inflammatory swellings, which would have gradually diminished with the regression of the lung tumor. These possibilities cannot be entirely ruled out. Another issue is whether we could definitively state that the tumor in the lung really represented metastasis from the tumor in the small intestine, and whether that tumor definitely originated from the small intestine. The detection of metastasis before a primary lesion and the origination of epithelioid angiosarcoma originating from the lung are both extremely rare events. Given the clinical course and the immunohistological characteristics that were observed in preparations of lung cell blocks and small intestinal tissue, we could definitively state that the histological characteristics of the tumor in the lung cell block preparations were compatible with those of the tumor in the small intestine. Based on this finding, it was considered likely that the epithelioid angiosarcoma originated from the small intestine.

The patient had a history of congenital pulmonary atresia. She had undergone X-ray, CT, and diagnostic cardiac catheterization many times and had thus her whole body had been exposed to high doses of medical radiation. Pulmonary valve disease, including pulmonary atresia is considered to occur in association with relatively high exposure (12). With regard to the cancer risk associated with radiation exposure in children with heart disease, several studies found that there was no demonstrable increase in cancer risk (13, 14). On the other hand, one study reported that children exposed to medical radiation show chromosomal damage after cardiac catheterization (15). Meanwhile, several cases of post-radiation soft-tissue sarcoma, including angiosarcoma, have been reported (16). One case involved the SR of breast angiosarcoma after breast-conserving therapy followed by radiotherapy for primary breast cancer (17). Needless to say, there are marked differences in the radiation doses used for diagnostic cardiac catheterization and for radiotherapy. There was no definitive evidence to support that this epithelioid angiosarcoma occurred as a result of exposure to medical radiation in childhood; however, it is possible that a link exists.

Conclusion

The present case involved the SR of epithelioid angiosarcoma of the small intestine, which was first detected as a

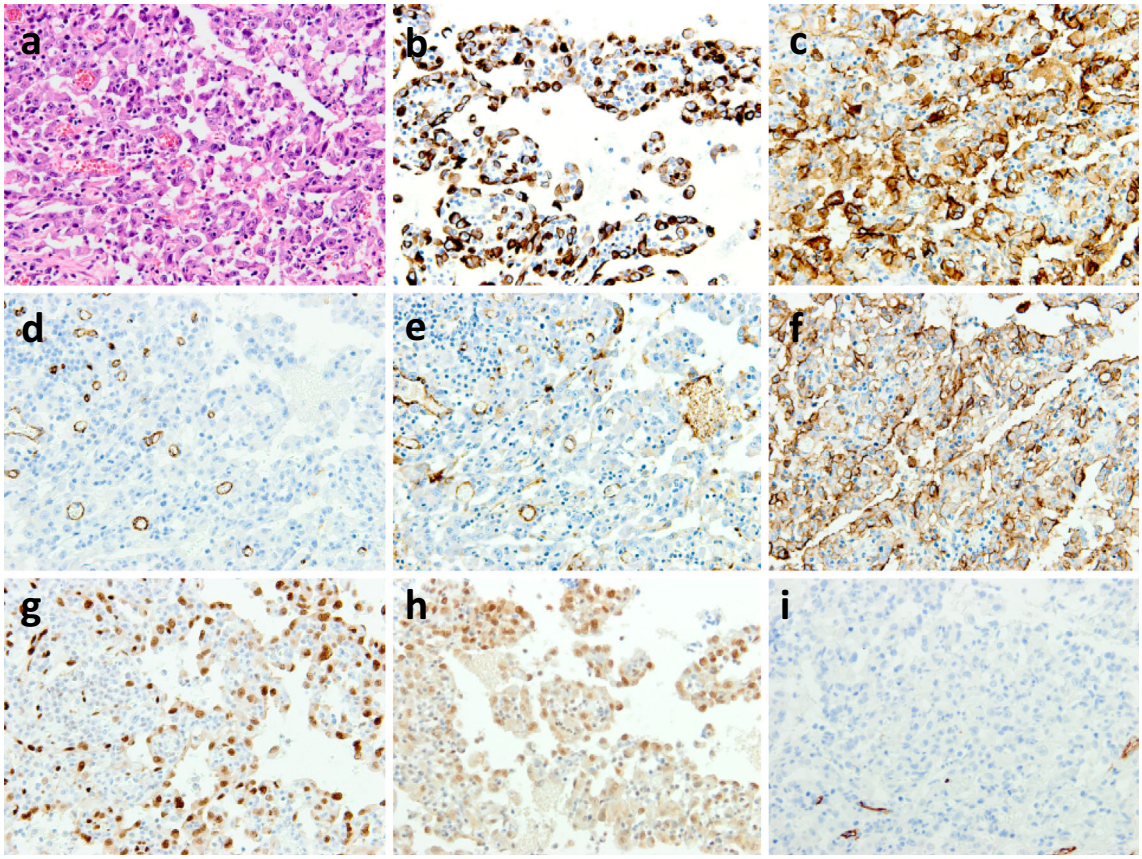

Figure 5. **A surgical specimen of the small intestine. The Hematoxylin and Eosin staining specimen (a). The immunohistological analysis revealed the following findings: CK CAM5.2-positive (b), CD31-positive (c), CD34-negative (d), factor VIII-negative (e), thrombomodulin-positive (f), ERG-positive (g), FLI-1-positive (h), and podoplanin-negative (i). CK: cytokeratin, ERG: ETS-related gene, FLI: friend leukemia integration**

metastatic lung lesion in a young woman exposed to medical radiation in childhood with a history of pulmonary atresia. The process of diagnosing this case was both histopathologically and clinically difficult.

The authors state that they have no Conflict of Interest (COI).

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