

Carcinoids of the Appendix: A Case Report, Combined with Statistical Analysis of 142 Cases of a Japanese Series

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Summary. A case of an appendiceal carcinoid in a 55-year-old female is described as a typical clinical and pathologic model, followed by a statistical analysis of 142 cases of appendiceal carcinoids reported in the Japanese and registered in the Niigata Registry. The analysis includes the incidence of appendiceal carcinoids, sex differences and age distribution, clinical manifestations, sizes of the tumors, metastases, the significance of silver impregnations, serotonin activity and an unusual histologic pattern of the goblet cell type and related varieties comprising 28.7% of the 142 appendiceal carcinoids. A statistical comparison was attempted between goblet cell carcinoids (Group A: n=43) and non-goblet cell carcinoids (Group B: n=98) when judged worthy of evaluation. Statistical significances were noted between these two groups in the male/female ratio, tumor-size distribution, rate of metastases and sites of involvement of the appendix. The low incidence of appendiceal carcinoids — 6.6% of 2,156 digestive carcinoids — as compared to carcinoids in other organs was thought to be largely influenced by background factors and not necessarily a faithful representation of the true occurrence of appendiceal carcinoids. Small-sized carcinoids measuring 10 mm or less comprised 60.0% of 95 cases. Of 76 cases with tumors 20 mm or less, 3 showed lymph node metastases and one had a focus of peritoneal involvement. The usefulness of silver impregnation techniques for diagnosing these tumors was reflected by a high rate of positive response of Grimelius' argyrophilia, indicating 93.7% of 63 cases, as well as by a high rate of argentaffin cell type variety showing 68.0% of 50 cases. The goblet cell type is further briefly discussed as a composite B and a histologic type C variety of carcinoid.

INTRODUCTION

It is well known that, among the digestive organs, carcinoids are relatively common in the appendix. In the authorized representative statistics of the US/European series of the digestive system, carcinoids of the appendix comprise a large portion of the series, ranging between 42.7% and 49.4%.¹⁻⁶⁾ In the Japanese series of reported cases,⁶⁾ the organ-distribution of carcinoids in the digestive system shows an incidence quite different from that of the US/European series. A significantly low incidence of organ-distribution of carcinoids in the Japanese series is found in the appendix, indicating 6.6% of 2,156 reported cases, as well as in the small intestine, showing 3.2%. It must, however, be pointed out that there are differing backgrounds or situations in collecting cases and that the organ-distribution of carcinoids is not necessarily a faithful representation of the occurrence of carcinoids. On the other hand, it is suggested that the above-mentioned explanation alone can not cover the statistically significant differences in the organ-distribution of carcinoids between the US/European and the Japanese series. It is thus possible that the Japanese tend to be significantly lower in not only incidence of the organ-distribution but also in the occurrence of appendiceal carcinoids.

This study aims to elucidate the present status of appendiceal carcinoids in the Japanese from varying clinicopathological aspects on the basis of 143 reported cases collected from the Niigata Registry.⁷⁾

CASE REPORT

One case is here described as a typical model for an

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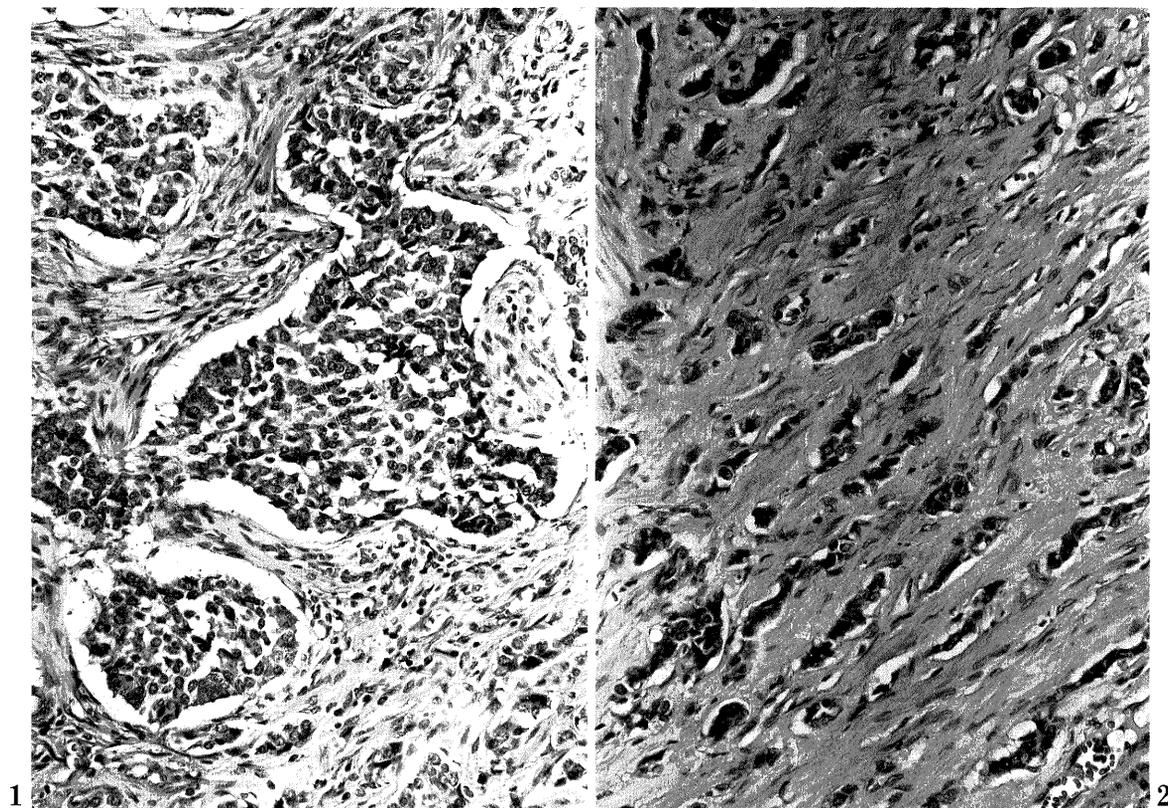


Fig. 1. The basic structural pattern of the neoplasm appears as nodular or insular solid nests with a surrounding rim of palisading cells typical for the type A category of histologic classification of carcinoids.⁸⁾ Hematoxylin and eosin. $\times 160$ (original magnification $\times 50$)

Fig. 2. Neoplastic cells at the periphery of the lesion—markedly distorted from the initial basic pattern—are transformed into a scirrhous pattern actively invading the muscular coat extensively replaced by a dense collagenous fibrous stroma. Hematoxylin and eosin. $\times 160$ (original magnification $\times 50$)

appendiceal carcinoid in the Japanese series.

Patient: M. S. A 54-year-old female complaining of epigastralgia and vomiting of two days' duration was admitted with a diagnosis of acute appendicitis. She had a moderate tenderness in the right lower quadrant of her abdomen. Her white blood cell count was 9,400.

An appendectomy was carried out and a gross diagnosis of acute gangrenous appendicitis was made. Histologic examination on tissue preparations stained with routine hematoxylin and eosin supported the gross diagnosis but further revealed a carcinoid replacing a small piece of tissue. The gross specimen was re-examined. The resected appendix measured $60 \times 15 \times 15$ mm, with the proximal half portion entirely involved by transmural suppurative inflammation with microabscesses and necrosis. The distal half portion was in large part replaced by a grayish firm neoplas-

tic tissue involving the serosal aspect, measuring 32 mm in length and 12 mm in width.

An ileocecal resection with regional lymphadenectomy was performed 25 days following the appendectomy.

The patient was discharged after an uneventful post-operative course. She developed a fist-sized serous cystadenocarcinoma in the left ovary with peritoneal dissemination and underwent left oophorectomy for palliation 2 years and 3 months after carcinoid surgery. She died 5 years after the appendectomy. Autopsy disclosed extensive metastases of the ovarian carcinoma, but no residual carcinoid tissue was identified.

Pathologic findings: the neoplasm consisted of sheets and islands of ovoid cells with regularly round nuclei, originating in the mucosa and invading the underlying submucosa and muscular coat down to the

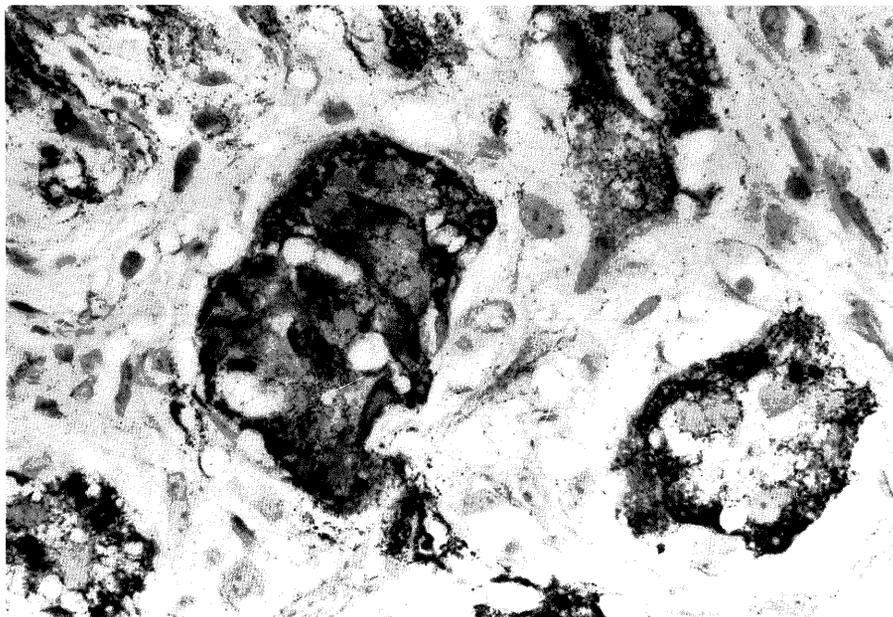


Fig. 3. Neoplastic cells in small nests invading the muscular coat show diffusely positive Grimelius' argyrophilia. $\times 600$ (original magnification $\times 200$)

serosa and mesoappendix. The basic histologic pattern of this neoplasm was typical for the type A carcinoid,⁸⁾ being composed of nodular or insular solid nests with a surrounding rim in a palisading cell arrangement (Fig. 1). Neoplastic cells at the periphery of the lesion were, however, markedly distorted from such a basic pattern and transformed into a scirrhous pattern actively invading the muscular coat extensively replaced by a dense collagenous fibrous stroma (Fig. 2). No Paneth cells were recognized. Lymphatic permeation by neoplastic cells was frequently noted. Both Grimelius' argyrophil (Fig. 3) and Fontana-Masson argentaffin stainings were strongly positive. Immunocytochemical examination with the peroxidase anti-peroxidase (PAP) method showed numerous positive cells for chromogranin, a few scattered positive cells for serotonin (5-hydroxytryptamine: 5-HT) and neuron specific enolase (NSE), and negative reaction for somatostatin, glucagon, gastrin, calcitonin, ACTH, insulin, pancreatic polypeptide (PP), vasoactive intestinal peptide (VIP), peptide tyrosine tyrosine (PYY), motilin, neurotensin, beta-endorphin, substance P, carcinoembryonic antigen (CEA) and S-100 protein.

The peritoneal lesion removed at the second laparotomy with the ileocecal resection was confirmed histologically to be a carcinoid identical to the primary neoplasm in the appendix; no involvement of lymph nodes was proved.

Electron microscopic observation was done on the

formalin-fixed paraffin-embedded tissue after its being re-fixed with glutaraldehyde and osmium tetroxide (OsO_4), and doubly-stained with uranyl acetate and lead citrate for electron microscopy. The neoplastic cells possessed a relatively clear cytoplasm with round to ovoid nuclei. The cytoplasmic organelles were in general poorly developed with abundant ribosomes and a few scattered small mitochondria. There were many well-preserved secretory granules of an endocrine type, mostly round and occasionally rod-shaped, measuring from 130 to 300 nm at most (Figs. 4 and 5). Occasional perinuclear regions contained bundles of a fine fibrillar structure of unknown origin (Fig. 5). Immunoelectron microscopy for 5-HT with post-embedding method (protein A-gold method) disclosed a few secretory granules with positive particles.

A final diagnosis of an A type, argentaffin cell carcinoid of the appendix with suppurative appendicitis was made.

MATERIALS AND METHODS

A statistical analysis was undertaken on 142 cases of appendiceal carcinoids collected from the Niigata Registry,^{6,7)} in which cases of gut-pancreatic endocrinomas are computerized in such a way that duplication of the cases can be avoided. All patients with gut endocrinomas (carcinoids) including those reported in foreign journals were confirmed as Japanese.

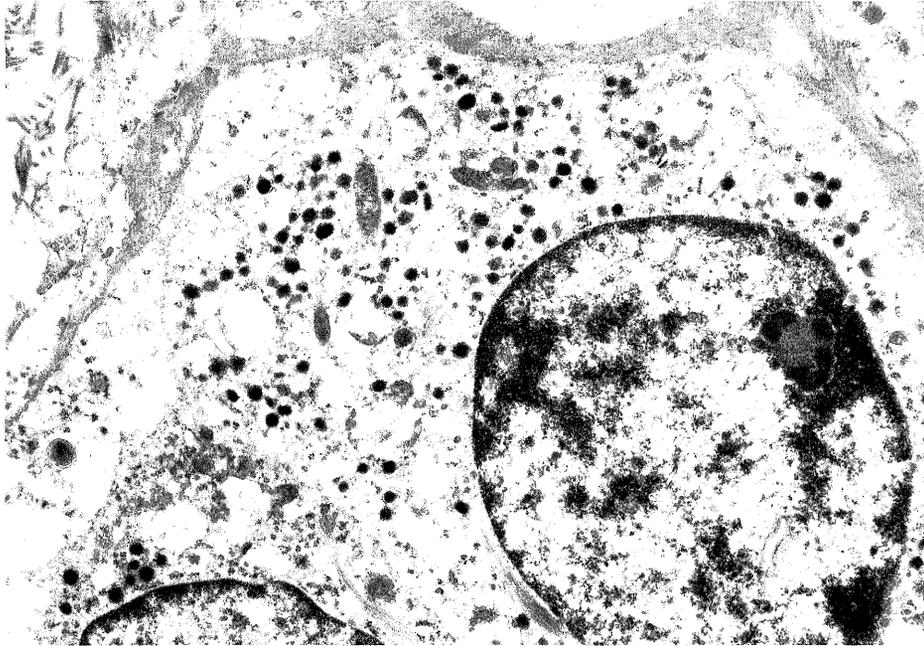


Fig. 4. Electron micrograph showing neoplastic cells with numerous secretory granules of the endocrine type. The endocrine granules are mostly round but occasionally rod-like in shape, ranging from 130 to 300 nm at most. Processed for electron microscopy from formalin-fixed paraffin-embedded tissue material; refixed with glutaraldehyde and osmium tetroxide. Uranyl acetate and lead citrate stain. Magnification: $\times 10,000$ (original magnification: $\times 6,000$)

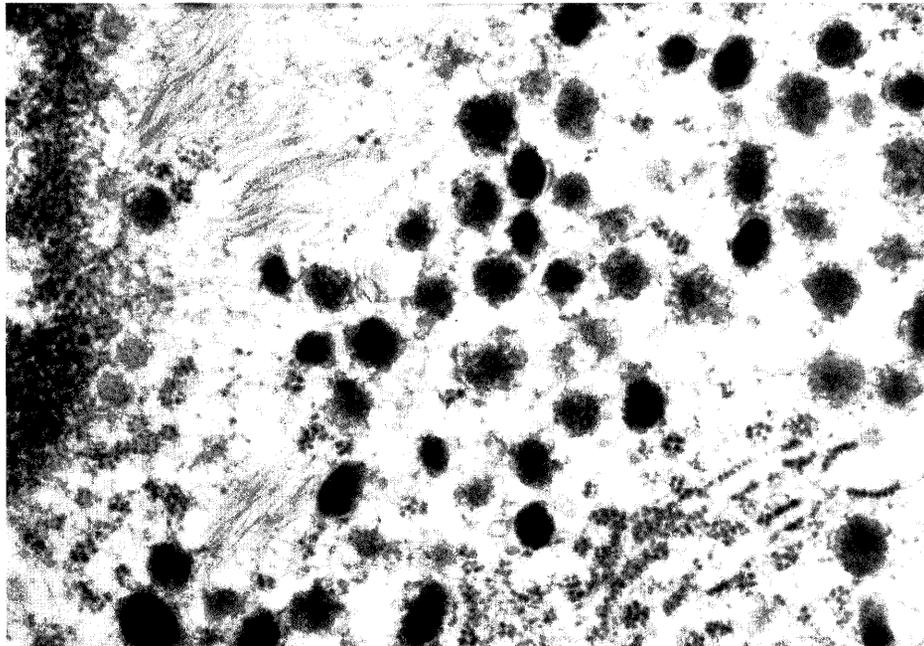


Fig. 5. Higher magnification of an electron-micrograph of a carcinoid cell indicates a fibrillar structure present in the perinuclear region at the left upper corner. Most granules are round or ovoid, though a few are rod-shaped. Processed for electron microscopy from formalin-fixed paraffin-embedded tissue material; refixed with glutaraldehyde and osmium tetroxide. Uranyl acetate and lead citrate stain. Magnification: $\times 35,000$ (original magnification: $\times 20,000$)

A statistical comparison was attempted between goblet cell carcinoids (Group A: n=43) and non-goblet cell carcinoids excluding a tubular type adenocarcinoid (Group B: n=98) when judged worthy of evaluation.

OBSERVATION AND DISCUSSION

1. Incidence of appendiceal carcinoids: Among 2,156 cases of gastrointestinal carcinoids of the Japanese series, appendiceal carcinoids comprised 6.6% (142/2,156),⁶⁾ whereas it is well known that the vermiform appendix is the site of the highest incidence of carcinoids in the US/European series.¹⁻⁶⁾ The significant difference between both series is explained as a result of the difference of the background in collecting cases.⁶⁾ While the low incidence of appendiceal carcinoids may not be a faithful representation of the true occurrence of these neoplasias, other factors such as racial or genetic constitution and circumstantial or environmental influences should be also taken into consideration, since in the Japanese autopsy series the incidence of appendiceal carcinoids, which might be expected to represent the approximately true occurrence of these neoplasias, exhibited a further low incidence of 2.5% (21/826) in the gastrointestinal carcinoid group.⁶⁾

Among appendectomy specimens, the incidence of carcinoids has been variably reported as ranging between 0.03% and 1.3%.⁹⁻¹²⁾

2. Male/female ratio and age-distribution: Female preponderance with a male/female ratio of 0.7 (58/82) was apparent in the appendiceal carcinoid group of the present series, whereas the overall male/female ratio was 1.5 (1,255/855) in the gastrointestinal carcinoid group.⁶⁾ The female preponderance is more apparent in one of the largest series dealing with 150 appendiceal carcinoids by the Mayo Clinic Group showing a male/female ratio of 0.4 (39/97).¹¹⁾ In the US series this is explained as being attributed to the incidental appendectomies in females who have gynecologic surgery,⁹⁾ and is reflected in the figure indicating a large ratio of gynecologic and gallbladder disease cases among all appendectomy cases (62.5%: 85/136).¹¹⁾

A male preponderance of 1.4 in Group A (n=41) was, however, statistically significant ($p < 0.01$) as compared to Group B (n=98), with a female preponderance of 0.5.

The average age in the appendiceal carcinoid group was 42.6 years for males and 37.5 years for females, ranging between 9 and 92 years, in comparison with the overall average in the gastrointestinal carcinoid

group of 54.4 years and 53.2 years,⁶⁾ respectively.

The comparative study between Group A (n=41) and Group B (n=97) exhibited an average age of 55.7 years in the former group and 33.3 years in the latter.

3. Clinical manifestations: Most cases of appendiceal carcinoids were found incidentally at histological examination following appendectomy under the diagnosis of acute appendicitis. Of 119 cases with descriptions of signs and symptoms, 101 (93.2%) were accompanied by abdominal pain, 25 (21.0%) by nausea/vomiting and 17 (14.3%) by fever. Histological confirmation of acute appendicitis was made in 66 (46.5%) of the 142 cases. This figure is significantly higher than the 12.5% (17/136) described in the Mayo Clinic Group's report.¹¹⁾

4. Site of involvement: Among 87 cases in which the site of involvement was described, the distal portion was found to be that of most frequent involvement by carcinoids, showing 74.7% (65/87) of the cases (Tables 1 and 4). It is well known that the tip of the appendix is the predominant site of carcinoids.¹¹⁻¹³⁾

The comparison between Group A (n=26) and Group B (n=60) showed a stronger tendency for diffuse involvement of the appendix in the former group than the latter (19.2% vs 5.0%: $p < 0.01$).

5. Tumor size: The size of appendiceal carcinoids was described in 95 cases; 57 (60.0%) of them were reported to show a size of 10 mm or less. One of the largest series of appendiceal carcinoids indicates 76.5% (104/136) of cases with a tumor size of 10 mm or less.¹¹⁾

The comparison between Group A (n=14) and Group B (n=80) indicated a significantly higher incidence of a small size of 10 mm or less in the former group and of a size between 11-20 mm in the latter ($p < 0.01$ and $p < 0.05$, respectively).

6. Metastases: Of 142 cases of appendiceal carcinoids, 19 (13.4%) were recorded to have metastases (Table 2). As to the correlation between tumor size and metastases in 95 cases with the size described, 4 cases (5.3%: 4/76) with tumors 20 mm and less and 7 (36.8%: 7/19) with tumors over 20 mm showed metastases (Tables 2 and 4). Among the former 4 Cases, 3 had lymph node metastases and 1 showed peritoneal involvement. Of 19 cases with metastases, 12 (63.2%) revealed tumor involvement in the peritoneum, 11 (57.9%) in lymph nodes, 6 (31.6%) in the ovary, 2 (10.5%) in the pancreas and 1 each (5.3%) in the liver and lung. Although the Mayo Clinic series declared

Table 1. Sites of appendiceal carcinoids

	Distal	Middle	Proximal	Distal/ Middle	Middle/ Proximal	Diffuse	Total
A	6 (23.1)	3 (11.5)	4 (15.4)	6 (23.1)	1 (3.8)	6 (23.1)	26 (100.0)
B	43 (70.5)	7 (11.5)	7 (11.5)	1 (1.6)	0 (0.0)	3 (4.9)	61 (100.0)
T	49 (56.3)	10 (11.5)	11 (12.6)	7 (8.0)	1 (1.1)	9 (10.3)	87 (100.0)

Figures in parentheses indicate %

A: Goblet cell carcinoids, B: Non-goblet cell carcinoids, T: Total/average

Table 2. Tumor size and metastases

Size (mm)	-10	-20	-50	51-	Subtotal	ND	Total
No. cases	57	19	10	9	95	47	142
	└───┬───┘ 76		└───┬───┘ 19				
With metastases	1	3	3	4	11	8	19
	└───┬───┘ 4		└───┬───┘ 7				
% Metastases	1.8	15.3	30.0	44.5	11.6	17.0	13.4
	└───┬───┘ 5.3		└───┬───┘ 36.8				

ND: Size not described.

that the patients with the larger tumors and metastases were younger than those with smaller and clinically benign tumors,¹¹⁾ the present study gave a reverse result, showing the average age of the small tumor (20 mm or less) group to be significantly younger than that of the larger-tumor group, 37.8 years versus 58.9 years, respectively. The rate of metastases was significantly higher in Group A (n=43) than in Group B (n=98) (23.3% vs 8.2%: p<0.05).

7. Silver impregnations: The rate of positive Grimelius' argyrophilia was 93.8% of 65 cases, suggesting the usefulness of this technique for diagnosis. This is in accordance with the results of a recent investigation.¹⁴⁾ Argentaffin cell type appendiceal carcinoids showed a significantly high incidence of 69.2% of 52 cases in which both Grimelius' argyrophilia and Fontana-Masson argentaffinity had been carried out. This incidence rate was significantly high as compared with the average in the entire carcinoid series, indicating 18.1% of 838 cases,⁶⁾ and identical to the value of 67% (12/18) recently reported.¹⁵⁾

8. Serotonin (5-hydroxytryptamine: 5-HT) activity: Serotonin activity represented by serum serotonin levels and urinary 5-HIAA (5-hydroxyindole

acetic acid) excretion in patients with carcinoids was recorded in 7 cases, with 3 of them showing elevated serotonin activity.

9. Carcinoid syndrome: Two suspicious cases of an appendiceal carcinoid with carcinoid syndrome were recorded in the series.^{6,7)} None showed complete or typical manifestations of the syndrome. The first case was a 22-year-old female with multiple appendiceal carcinoids who suffered from episodes of flushing and swelling around the eyes accompanied by an abnormal increase in histamine metabolism, suggesting the flushing episodes to be of a histamine origin. The second case was an 18-year-old female whose argentaffin cell carcinoid of the appendix had been associated with facial flushing episodes which disappeared after appendectomy and were reported as an appendiceal carcinoid with "flushing syndrome".

It is well known that appendiceal carcinoids are rarely associated with carcinoid syndrome. In one of the statistical works, all 5 cases of appendiceal carcinoids with carcinoid syndrome are reported to have metastases.¹⁰⁾

10. Goblet cell type and related varieties: Appendiceal carcinoids producing a significantly large

Table 3. Comparison of appendiceal carcinoids with goblet cell and non-goblet cell varieties

	A (n=43)	B (n=98)	Statistical significance
Male/female ratio	1.4 (41)	0.5 (98)	p<0.01
Average age (years)	55.5 (41)	32.8 (97)	p<0.001

Clinical manifestations	%	%	
Abdominal pain	87.8	96.1	NS
Nausea/vomiting	12.2 (41)	26.0 (77)	NS
Site			
Distal	65.4	78.3	NS
Diffuse	19.2 (26)	5.0 (60)	p<0.05
Tumor size			
-10 mm	14.3	68.8	p<0.01
11-20 mm	42.9 (14)	16.3 (80)	p<0.05
Metastases	23.3 (43)	8.2 (98)	p<0.05
Grimelius argyrophilia	96.6 (29)	91.7 (36)	NS
Argentaffin cell type	68.2 (22)	70.0 (30)	NS

A: Goblet cell carcinoids

B: Non-goblet cell carcinoids excluding a tubular type adenocarcinoma

NS: No statistical significance demonstrated

Figures in parentheses indicate the number of cases examined

amount of mucus are designated as goblet cell carcinoids,¹⁶⁾ mucinous carcinoids,¹⁷⁾ one of two subtypes of adenocarcinoids,¹⁸⁾ crypt cell carcinoma,¹⁹⁾ or a signet-ring cell carcinoma, not only in the appendix²⁰⁾ but also in the liver.²¹⁾ Carcinoids of this particular type are well explained as a composite B²²⁾ and type C⁸⁾ variety of carcinoid.⁶⁾

A statistical comparison was attempted between 43 goblet cell carcinoids (Group A) and 98 non-goblet cell carcinoids excluding an adenocarcinoid of the tubular type (Group B), and the results are summarized in Table 3.

A detailed analysis of 170 goblet cell carcinoids collected from the literature mainly from the United States, Europe and Japan has been published in a separate report.²³⁾

COMMENTS

Since most appendiceal carcinoids are incidentally

Table 4. Summary of appendiceal carcinoids

1. Incidence	6.6% (142/2,156) of GI series
2. Sex and age	
Male/female ratio	0.7 (58/ 82)
Age: Average Overall	39.6 years
Male	42.6
Female	37.5
Range	9-92
3. Clinical manifestations	
Abdominal pain	93.2% (111/119)
Nausea/vomiting	21.0% (25/119)
Fever	14.3% (17/119)
[Acute appendicitis	46.5% (66/142)]
4. Site of involvement:	
Distal portion	74.7% (65/ 87)
Distal portion only	56.3%
Distal and middle	8.0%
Diffuse	10.3%
5. Size: 10mm or less	60.0% (57/ 95)
6. Metastases	13.4% (19/142)
Size (n=95):	
-20 mm	5.3% (4/ 76)
21 mm -	36.8% (7/ 19)
19 cases with metastases:	
Peritoneum	63.2%
Lymph nodes	57.9%
Ovary	31.6%
Pancreas	10.5%
Liver	5.3%
Lung	5.3%
7. Silver impregnations	
Grimelius argyrophilia	93.8% (61/ 65)
Argentaffin cell type	69.2% (36/ 52)
Argyrophil cell type	28.8% (15/ 52)
Non-reactive cell type	1.9% (1/ 52)
8. Elevated serotonin activity	(3/ 7)
9. Carcinoid syndrome	0.0% (0/142)
Suspicious	1.4% (2/142)
10. Goblet cell/related varieties	30.3% (43/142)

GI: gastrointestinal

found at postoperative histologic examination in the acutely inflamed appendix—with a few discovered in the normal appearing appendix removed at other surgery, often gynecologic—a description of the size, site and depth of invasion is not recorded in most cases. Because of the small size of 10 mm or less in 60% of 95 cases, the rate of metastases is relatively low and most cases have been regarded as benign. Such a consideration, however, seems unlikely because the histology of appendiceal carcinoids constantly shows an aggressive invasion of the neoplastic cells in the appendiceal wall regardless of the

tumor size, and often a scirrhous invasion in the muscular layer with a dense fibrous stroma as shown in Fig. 2. Perineural permeation or lymphatic invasion is not an unusual finding in appendiceal carcinoids, even though they appear cytologically benign. Since carcinoid formation is known to occur in the basal portions of the glands in the mucosa,^{12,19,24)} any carcinoid found in the submucosa with or without deeper layer involvement should be considered an invasive neoplasm. Although it is well known that the prognosis of the patients with appendiceal carcinoids is considerably better than that of patients with carcinoids of any other organ,⁵⁾ one should consider the smaller size of most appendiceal carcinoids at detection when, however, they already have a great capability for lymphatic invasion and metastases.

Although it was concluded that simple appendectomy was adequate treatment for patients with apparently localized tumors with sizes smaller than 20 mm in their largest dimension,¹¹⁾ the results of the present study indicate that this might not always be adequate because of the occasional involvement of lymph nodes and peritoneum in patients with tumors with sizes of 20 mm or less as shown in Tables 2 and 4. Other than sizes greater than 20 mm and base localization, it is emphasized that the secondary right hemicolectomy is an indication for mucin-producing appendiceal carcinoids or abenocarcinoids based on the analysis of a large series of a collaboration study dealing with 181 appendiceal carcinoids.¹³⁾

The main features of appendiceal carcinoid analyses in the present study are summarized in Table 4.

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