Secondary tumors of the intestines in females: A retrospective clinicopathologic study of seven cases

A. Kondi-Pafiti[1], *M.D., Ph.D.*; **D. Grapsa**[1], *M.D.*; **D. Hasiakos**[2], *M.D., Ph.D.*; **V. Smyrniotis**[3], *M.D., Ph.D.*

[1]*Pathology Laboratory,* [2]*2nd Clinic of Obstetrics and Gynecology,* [3]*2nd Clinic of Surgery, University of Athens, Aretaieion Hospital, Athens (Greece)*

Summary

Objective: To investigate the primary site and the pathological features of secondary intestinal tumors in females, with emphasis on their differential diagnosis from primary neoplasms of the intestines.

Methods: Seven cases of secondary intestinal tumors in females were retrieved from the archival files of our laboratory. The relative clinical data were also reviewed. Inmmunohistochemistry was performed in cases with diagnostic difficulties.

Results: The primary site of the tumor was defined as follows: the ovary (ovarian adenocarcinoma) in five cases (71.4%), the skin (cutaneous malignant melanoma) in one case (14.28%) and the uterine corpus (mixed mullerian tumor) in one case (14.28%). In two cases the primary site was not determined initially, but the investigation showed that the primary tumor was ovarian in origin. In five cases the existence of a primary tumor was already known. Immunohistochemistry was applied in three cases for confirmation of the suspected primary tumor by histological examination.

Conclusion: Histological diagnosis of secondary intestinal tumors may be extremely difficult, especially when the primary site is not previously known, and because of the tendency of certain secondary tumors to mimic, both grossly and microscopically, the primary ones. Immunohistochemistry is extremely helpful in resolving these diagnostic difficulties.

Key words: Secondary tumors; Intestines; Ovarian adenocarcinoma; Differential diagnosis; Immunohistochemistry.

Introduction

Secondary tumors of the intestines are defined as intestinal tumors originating from an extra-intestinal neoplasm, or which are discontinuous with a primary gastrointestinal tumor [1]. The large bowel is only rarely affected by metastatic disease, while in the small intestine metastatic tumors outnumber the primary ones, with malignant melanoma accounting for the majority (50-70% approximately) of the secondary tumors of the small bowel and 10% of all intestinal metastases [2, 3]. Cancerous cells usually spread to the intestines hematogeneously when the primary site is located in distant organs such as the breast, the lung, the larynx, the bones, the thyroid gland or skin, or after local invasion from primary tumors of neighbouring organs (e.g. pancreatic carcinoma extending to the duodenum, and prostate or ovarian carcinoma to the rectum) [1, 2, 4-9].

Most patients with intestinal metastases are initially asymptomatic, or have non-specific symptoms such as generalized abdominal pain or discomfort, diarrhea or weight loss [1, 10, 11]. Small bowel involvement in particular may present with symptoms of appendicitis, malabsorption or protein losing enteropathy [12]. As a result, secondary intestinal tumors may not be suspected and remain undiagnosed even after endoscopic or radiological examination [10, 13]. The disease usually presents in advanced stages with acute abdominal symptomatology (intestinal bleeding, bowel occlusion or perforation) often requiring urgent surgical intervention [4, 5, 10].

Revised manuscript accepted for publication June 15, 2005

Materials and Methods

Formalin-fixed, paraffin-embedded tissues from secondary intestinal tumors, collected and stored over the last 15 years, were retrieved from the archival files of our laboratory. The relative clinical records were also reviewed. All slides were examined by two independent pathologists. Additional tissue sections were obtained for the application of a streptavidin biotin immunohistochemical study in cases with diagnostic difficulties. The primary antibodies used in this study were: S100 (MoAb), HMB45 (MoAb), NK1 (MoAb/C3), EMA (MoAb) LCA (MoAb) CA19.9 (MoAb), Cytokeratin CK7, Cytokeratin CK20, CEA and CA125.

Results

Seven cases of secondary intestinal tumors in a total of 600 colectomies were retrieved from the archival files of our laboratory and reevaluated. All patients were females and their age ranged from 53 to 88 years with a mean of 65.57 years. They were diagnosed with metastatic intestinal disease, either in the large or small bowel, with the exception of two patients with synchronous involvement of the large and small intestine. The primary site of the tumor was defined as follows: the ovary (ovarian adenocarcinoma) in five cases (71.4%), the skin (cutaneous malignant melanoma) in one case (14.28%) and the uterine corpus (mixed mullerian tumor) in one case (14.28%). In two cases the primary site was not initially determined, but the investigation showed that the primary tumor was ovarian in origin. In five cases the existence of a primary tumor was already known. Immunohistochemistry was applied in three cases for confirmation of the suspected primary tumor by histological examination (Table 1).

Table 1. — *Comparison of mean microvessel counts.*

Case (Age)	Material	Primary site	Histophatol. diagnosis	Immuno-histochemistry
1 (64)	Right semi-colectomy	Cutaneous malignant melanoma	Metastatic malignant melanoma of the ascending colon	S100(+) HMB45(+) NK1(+) EMA(-) LCA (-)
2 (65)	Small bowel section	Uterine corpus mixed mullerian tumour with etelo-logous elements	Spindle cell sarcoma or chondrosarcoma	–
3 (51)	Small bowel section Sigmoid colon	Could not be determined	Adenocarcinoma, secondary from ovarian primary (additional study)	CA 19.9, CK7(+) CK20 (-), CEA (-), CA125(+)
4 (88)	Small bowel section Large bowel section	Ovarian adenocarcinoma	Metastatic (ovarian) serous papillary adenocarcinoma	–
5 (58)	Small bowel section	Ovarian adenocarcinoma	Metastatic (ovarian) serous papillary adenocarcinoma	–
6 (53)	Large bowel section	Ovarian adenocarcinoma	Metastatic (ovarian) serous papillary adenocarcinoma	–
7 (80)	Left semi-colectomy	Unknown (possibly ovarian adenocarcinoma)	Metastatic (ovarian) mucinous adenocarcinoma	CA19.9(+) CK7(+) CK20(-) CEA(-) Ca125(+)

Discussion

Secondary intestinal tumors typically occur in patients with widespread malignant disease and synchronous metastases to sites other than the gastrointestinal tract [10]. However, early diagnosis of these neoplasms is extremely important not only for the avoidance of their life-threatening complications, such as bowel occlusion or perforation, but also for designation of the appropriate therapy and improvement of the quality of life [14-16]. Bowel perforation in patients with intestinal metastasis has also been associated with adjuvant chemotherapy for the primary tumor [4]. This fact indicates the need for extreme caution during chemotherapy in patients with possible secondary gastrointestinal tumors [4].

The histological diagnosis of secondary intestinal tumors may be extremely difficult especially when the site of primary malignancy is unknown [2]. Therefore, pertinent clinical information is indispensable for the correct evaluation of the histological findings. Secondary neoplasms of the intestines do not present any pathognomonic macroscopic appearance. They may appear macroscopically as ulcers, nodules, polyps, thickening of the

ig. 1

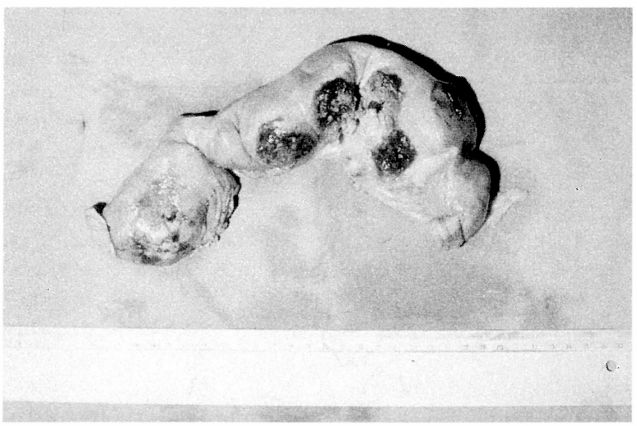
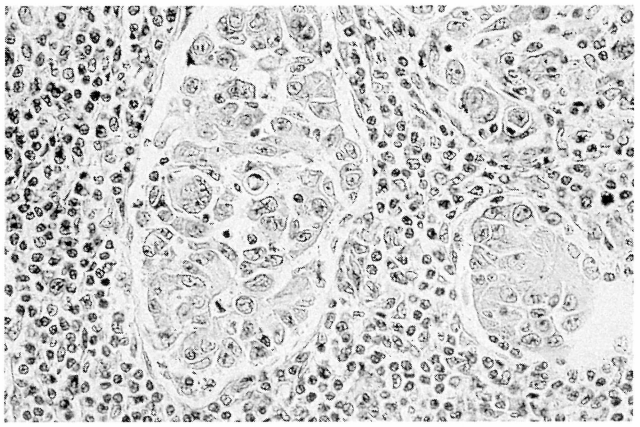


Fig. 2



g. 3

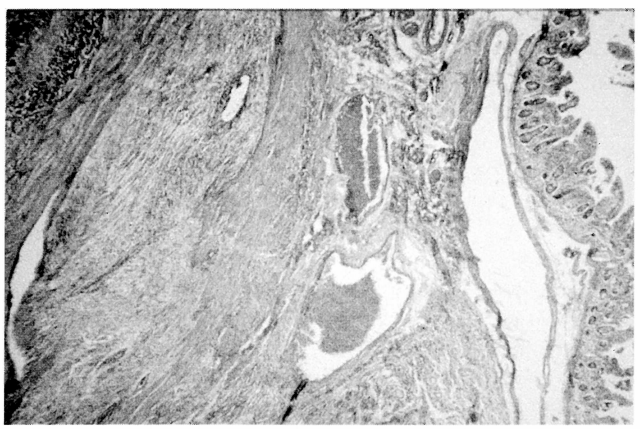


Fig. 4

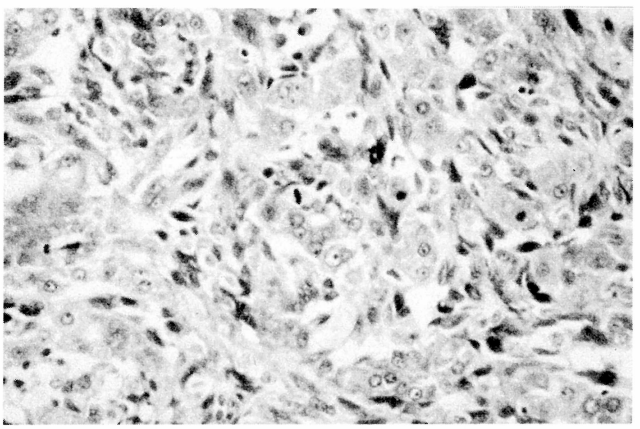
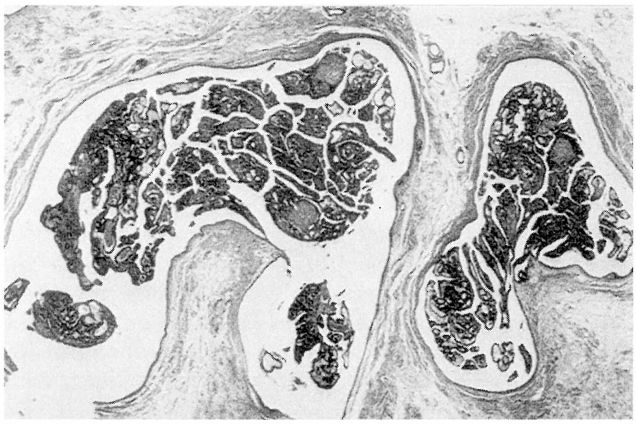


Figure 1. — Colonic specimen showing metastatic nodules of malignant melanoma (case 1).
Figure 2. — Histological section of colonic malignant melanoma showing dense lymphocytic infiltration around tumor cells (case 1) (hematoxylin-eosin x 250).
Figure 3. — Histological section of the small bowel wall showing a malignant neoplasm infiltrating the muscular wall (case 2) (hematoxylin-eosin x 250).
Figure 4. — The same case (case 2) under higher magnification showing metastatic sarcoma infiltrating the bowel wall (hematoxylin-eosin x 250).

Fig. 5



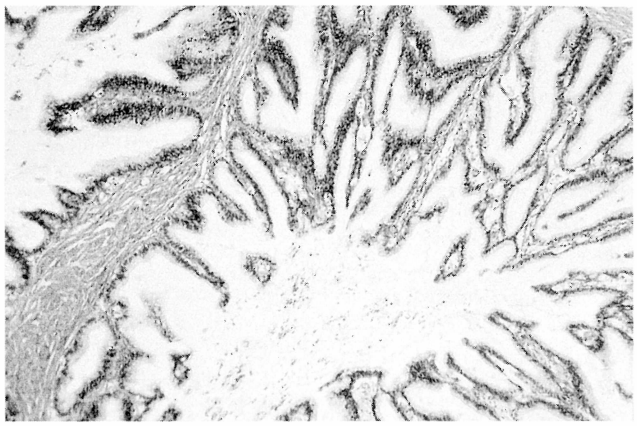


Fig.

Figure 5. — Ovarian serous papillary carcinoma infiltrating the mesocolic fatty tissue (case 4) (hematoxylin-eosin x 250).
Figure 6. — Histological section of metastatic adenocarcinoma infiltrating the colonic muscular wall (case 7) (hematoxylin-eosin x 250).

intestinal wall, or large extrinsic tumor masses [1, 17]. Their typical microscopic features include a subserosal location of the tumor with extension to the muscular wall or even a submucosal location with mucosa usually free of neoplastic infiltration [1, 18]. Metastasis to the bowel mucosa is not a typical finding, but still possible, and may occur by invasion of the serosal surface or infiltration of the submucosal papillary network, even with no involvement of the intestinal wall [19]. In three of our cases of intestinal metastases from ovarian adenocarcinoma the tumor extended throughout the whole intestinal wall, including the mucosa. Only in two cases was the mucosa intact. Involvement of the mucosa was also noticed in our two cases of metastatic melanoma and chondrosarcoma. These findings suggest that mucosa involvement in metastatic intestinal tumors may not be a rare finding, especially in late stages of disease.

Problems in diagnosis may arise when secondary tumors mimic primary ones both grossly and microscopically [2]. Metastatic melanoma exhibits a wide range of histological patterns of growth that may resemble carcinoma, sarcoma, carcinoid and large cell lymphoma [2]. Diagnosis may be even more problematic when melanoma is not pigmented [2]. In one of our studied cases (case 1) with metastatic melanoma in the large bowel (Figure 1), diagnosis was made after co-evaluation of the history of malignant melanoma, the histological findings (spindle shaped and epithelioid cells with atypical hyperchromatic nuclei and abundant melanin) (Figure 2) and the results of the immunohistochemical examination (Table 1). Another interesting case from our files (case 2) was a small bowel tumor presenting the morphological features of spindle cell sarcoma and chondrosarcoma and originating from a mixed mullerian tumor of the uterine corpus with heterologous elements (Figures 3 and 4). In one of our cases (case 3) it could not be pathologically defined, whether the tumor was a colonic cancer with ovarian metastases or an ovarian carcinoma extending to the large bowel due to widespread disease and loss of tumor differentiation. Additional immunohistochemical studies showed that this colonic tumor was ovarian in origin.

Three of our studied cases (cases 4, 5 and 6) of secondary intestinal tumors were considered as metastatic serous ovarian adenocarcinoma (Figure 5) and one case (case 7) as metastatic mucinous ovarian adenocarcinoma (Figure 6). In two cases there was synchronous involvement of the large and small intestine. Epithelial ovarian cancer spreads to the intestines mostly via intraperitoneal seeding [19]. However, hematogenous spread has also been reported and has been associated with the presence of advanced peritoneal disease. In women with late stage ovarian cancer, intestinal wall metastases are commonly found and tend to be multifocal [21]. Because of the similar histological patterns of growth (mucus producing cells, large cystic glands) shown by certain mucinous ovarian adenocarcinomas and colonic carcinoma, the differential diagnosis between a primary intestinal tumor and a tumor metastasizing from the ovaries may require the application of immunohistochemistry, especially when the clinical history is absent, inadequate or unreliable [19, 22, 23]. Cytokeratin immunohistochemistry may help to differentiate between primary colon cancer (positive for cytokeratin 20, negative for cytokeratin 7) and metastases from the ovary (positive for cytokeratin 7, negative for cytokeratin 20) [19, 24]. Useful markers also include CA19.9 and CA125 which are typically positive in cases of metastases from the ovaries [25]. A novel marker recently introduced in the differential diagnosis between primary and metastatic colonic adenocarcinoma is CDX-2, a transcription factor involved in the proliferation and differentiation of intestinal epithelium [25, 26-68]. CDX-2 is considered as a specific marker of intestinal adenocarcinoma, even though it can also be expressed in certain exta-intestinal adenocarcinomas, such as mucinous ovarian or urinary bladder adenocarcinoma [26].

We performed immunohistochemical analysis in two cases (cases 3 and 7) out of the five suspected ovarian metastases because the primary tumor was not previously known and could not be determined on the basis of the pathological findings alone. Immunohistochemistry showed a typical immunophenotype of ovarian adenocarcinoma (CK7 +, CK20 -, CA19.9 +, CA125+, CEA-). In

the remaining three cases the diagnosis of metastatic ovarian adenocarcinoma was based on the microscopic examination, history of previous ovarian malignancy and metachronous intestinal involvement.

Immunohistochemistry may help resolve most cases with diagnostic difficulties in the differential diagnosis between a primary and a secondary tumor. Nonetheless, its own limitations are not lacking, resulting mainly from the overlapping of certain immunohistochemical phenotypes between different neoplasms [2]. For example, in cases of prostatic adenocarcinoma extending to the rectum, the application of immunohistochemistry is needed to determine the site of the primary tumor because of the tendency of prostate carcinoma cells to form annular strictures resulting from circumferential infiltration, thus simulating – grossly and microscopically – a primary intestinal tumor [2, 29]. Extension of prostate carcinoma to the rectum may also mimic primary rectal carcinoid [2]. However, the majority of rectal carcinoids are positive for prostate acid phosphatase, while, on the other hand, prostatic carcinomas may contain endocrine cells [2, 30, 31]. In the latter case, the differential diagnosis requires the demonstration of PSA (prostate specific antigen), which is typically negative in primary carcinoids and positive in prostate metastasis. Another example is the marker CDX-2 which is mainly expressed in intestinal but also in ovarian and urinary bladder adenocarcinomas, as previously mentioned. It should be therefore stressed that the results of the immunohistochemical examination should always be evaluated with caution and with direct comparison to the histological findings and clinical information.

Conclusion

Secondary intestinal tumors are typically found in patients with advanced malignant disease, and should be diagnosed early to avoid life-threatening complications, designation of the appropriate therapy and allow improvement of the quality of life. Patients with gastrointestinal symptoms and a history of previous malignancy should therefore be thoroughly investigated for the presence of intestinal metastasis. The histological diagnosis of these neoplasms may be extremely difficult, especially when the site of the primary malignancy is unknown or when the secondary tumors mimic the primary ones. Immunohistochemistry is extremely helpful in the differential diagnosis between a primary and a secondary intestinal tumor, and should always be correlated with the histological findings and the information provided by the attending physician.

References

[1] Niederau C., Sobin L.H.: "Secondary tumors of the small and large intestines". In: Hamilton S.R., Aaltonen L.A. (eds.). World Health Organization Classification of tumors. Pathology and Genetics of Tumors of the Digestive System. Lyon: IARC Press, 2000, 91.

[2] Riddell R.H., Petras R.E., Williams G.T., Sobin L.H.: "Metastatic and other secondary tumors". In: Rosai J. (ed.). Atlas of Tumor Pathology. Tumors of the Large Intestines. Bethesda, Maryland. AFIP, 2003, 431.

[3] Backman H.: "Metastases of malignant melanoma in the gastrointestinal tract". *Geriatrics.*, 1969, *24*, 112.

[4] Hata K., Kitayma J., Shinozaki M. *et al.*: "Intestinal perforation due to metastasis of breast carcinoma, with special reference to chemotherapy: a case report". *Jpn. J. Clin. Oncol.*, 2001, *31,* 162.

[5] Cappabianca S., Barberi A., Gallo M., Del Vecchio W., Grassi R.: "Small bowel metastases of lung cancer as unique metastatic lesions: CT, MRI and small bowel enema findings. A case report". *Tumori*, 2002, *88,* 68.

[6] Buyukcelik A., Ensari A., Sarioglu M., Isikdogan A., Icli F.: "Squamous cell carcinoma of the larynx metastasized to the ampulla of Vater. Report of a case". *Tumori,* 2003, *89*, 199.

[7] Tamura M., Oda M., Ohta Y., Omura K., Nonomura A., Watanabe G.: "Small intestinal bleeding, secondary to metastatic malignant fibrous histiocytoma of the rib: report of a case". *Surg. Today,* 2002, *32,* 69.

[8] Bandorski D., Arps H., Jaspersen D., Diehl K.L.: "Severe intestinal bleeding caused by intestinal metastases of a primary angiosarcoma of the thyroid gland". *Z. Gastroeneterol.*, 2002, *40,* 811.

[9] Mehta N., Shetty T.S., Suhas U., Patnaik P.S., Joshi R.: "Metastatic amelanotic melanoma". *Indina J. Gastrenterol.*, 2002, *21,* 160.

[10] Ledermann H.P., Binkert C., Frohlich E., Borner N., Zollikofer C., Stuckmann G.: "Diagnosis of symptomatic intestinal metastases using transabdominal sonography and sonographically guided puncture". *AJR Am. J. Roentgenol.*, 2001, *176,* 155.

[11] Marin M., Vlad L., Grigorescu M., Sparchez Z., Dumitra D., Muti L.: "Metastasis of malignant melanoma in the small intestine. A case report". *Rom. J. Gastroenterol.*, 2002, *11,* 53.

[12] Branum G.D., Seigler H.F.: "Role of surgical intervention in the management of intestinal metastases from malignant melanoma". *Am. J. Surg.*, 1991, *162,* 428.

[13] Elsayed A.M., Albahra M., Nzeako U.C., Sobin L.H.: "Malignant melanoma in the small intestine: a study of 103 patients". *Am. J. Gastroenterol.*, 1996, *91,* 1001.

[14] Villavicencio H.: "Quality of life of patients with advanced and metastatic prostatic carcinoma". *Eur. Urol.*, 1993, *24* (suppl. 2), 118.

[15] Guillem P., Brygo A., Assila C., Dabrowski A.: "Small bowel metastases from head and neck cancers". *Ann Chir.,* 2004, *129,* 422.

[16] Peng Z., Pan X., Liu H.: "Surgical treatment of ovarian malignant tumors metastasized to the gastro-intestinal tract: a report of 131 cases". *Zhonghua Zhing Liu Za Zhi.*, 1999, *21*, 142.

[17] Ihde J.K., Coit D.G.: "Melanoma metastatic to stomach, small bowel, or colon". *Am. J. Surg.*, 1991, *162,* 208.

[18] Rosai J., Ackerman L.V.: "Large bowel". In: Rosai J. (ed.), "Surgical Pathology". Edinburgh, Mosby, 200, 1704.

[19] Zighelboim I., Broaddus R., Ramirez P.T.: "Atypical sigmoid metastasis from a high-grade mixed adenocarcinoma of the ovary". *Gynecol. Oncol.*, 2004, *94,* 850.

[20] Trastour C., Rahili A., Schumacker C., Effi A.B., Bernard J.L. : "Hematogenous rectal metastasis 20 years after removal of epithelial ovarian cancer". *Gynecol. Oncol.*, 2004, *94,* 584.

[21] Dvoretsky P.M., Richards K.A., Bonfiglio T.A.: "The pathology and biologic behaviour of ovarian cancer. An autopsy review". *Pathol Annu.,* 1989, *24*, 1.

[22] Taal B.G., Hageman P.C., Delemarre J.F., Bonfrer J.M., den Hartog, Jager F.C.: "Metastatic ovarian or colonic cancer: a clinical challenge". *Eur J Cancer,* 1992, *28*, 394.

[23] Killic G., Abadi M.: "Jejunal adenocarcinoma presenting as a primary ovarian carcinoma". *Gynecol. Oncol.,* 2000, *78,* 255.

[24] Park S.Y., Kim H.S., Hong E.K., Kim W.H.: "Expression of cytokeratins 7 and 20 in primary carcinomas of the stomach and colorectum and their value in the differential diagnosis of metastatic carcinomas to the ovary". *Hum. Pathol.,* 2002, *33,* 1078.

[25] Raspollini M.R., Ammuni G., Villanucci A., Baroni G., Taddei A., Taddei G.L.: "Utility of CDX-2 in distinguishing between primary and secondary (intestinal) mucinous ovarian carcinoma: an immunohistochemical comparison of 43 cases". *Appl. Immunohistochem. Mol. Morphol.,* 2004, *12,* 127.

[26] Werling R.W., Yaziji H., Bacchi C.E., Gown A.M.: "CDX-2, a highly sensitive and specific marker of adenocarcinomas of intestinal origin: an immunohistochemical survey of 476 primary and metastatic carcinomas". *Am. J. Surg. Pathol.*, 2003, *27*, 303.
[27] Fraggetta F., Pelosi G., Cafici A., Scollo P., Nuciforo P., Viale G.: "CDX-2 immunoreactivity in primary and metastatic ovarian mucinous tumors". *Virchows Arch.*, 2003, *443*, 782.
[28] Saad R.S., Essig D.L., Silverman J.F., Liu Y.: "Diagnostic utility of CDX-2 expression in separating metastatic gastrointestinal adenocarcinomas from other metastatic adenocarcinoma in fine-needle aspiration cytology using cell blocks". *Cancer*, 2004, *102*, 168.
[29] Culkin D.J., Demos T.C., Wheeler J.S., Castelli M., Canning J.R.: "Separate annular strictures of the rectosigmoid colon secondary to unsuspected prostate cancer". *J. Surg. Oncol.*, 1990, *43*, 189.
[30] Kimura N., Sasano N.: "Prostate-specific acid phosphatase in carcinoid tumors". *Virchows Arch A Pathol Anat Histopathol.*, 1986, *410*, 247.
[31] Sobin L.H., Hjermstad B.M., Sesterhenn I.A., Helwig EB.: "Prostatic acid phosphatase activity in carcinoid tumors". *Cancer*, 1986, *58*, 136.

Address reprint requests to:
A. KONDI-PAFITI, M.D., Assoc. Prof.
Pathology Laboratory
Aretaieion Hospital
Vas Sofias, 76
Athens 11528 (Greece)