Pathology and Differential Diagnosis

29

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Contents

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29.1 Gastrointestinal Stromal Tumor

29.1.1 Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumor of the gastrointestinal tract (Figs. 29.1–29.5). They primarily affect middle-aged or older adults, and they occur only rarely in children and adolescents. It has been proposed that GIST arises from the interstitial cells of Cajal (Liegl-Atzwanger et al. 2010; Benesch et al. 2009; Kaemmer et al. 2009; Machairas et al. 2010; Shimomura et al. 2010). Besides GIST, the family of mesenchymal tumors includes plexosarcomas, leiomyoblastomas, leiomyosarcomas (LMS), gastrointestinal autonomic nerve tumors (GANT), and gastrointestinal pacemaker cell tumors (GIPACT). While extensive research has been done on adult GIST by the National Comprehensive Cancer Network, the European Society of Medical Oncology, and others, standard practice and guidelines for children affected by GIST have not yet been established (Benesch et al. 2009).

29.1.2 Presentation

Pediatric GIST is most commonly found in the stomach (typically in the antrum), although cases have been identified in the small intestine, colon/rectum, omentum, and abdominal wall (Benesch et al. 2009; Shimomura et al. 2010). The average size of the tumor is 5.7 cm in greatest dimension with a range of 1.5–35 cm. Some patients, even unaffected by an associated tumor syndrome, present with multiple tumors or tumors with numerous satellite lesions. Metastasis is not uncommon, and it typically presents in the liver

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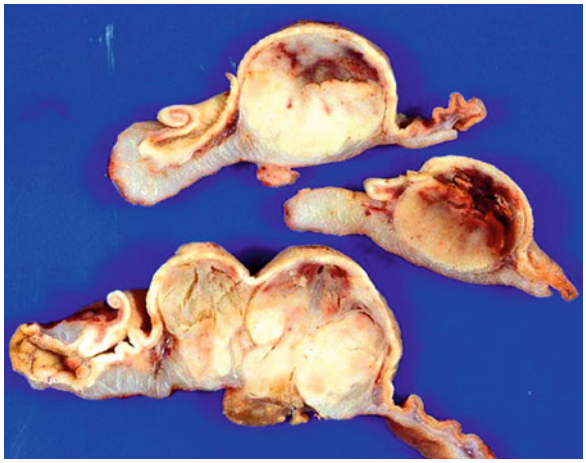

Fig. 29.1 Gastrointestinal stroma tumor: Multiple submucosal nodules showing gray–tan myxoid cut surface

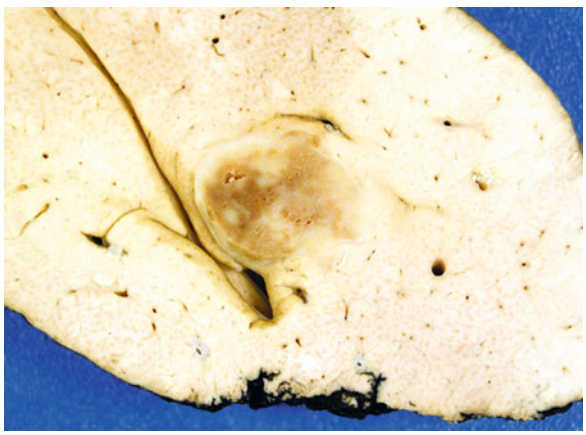

Fig. 29.2 Gastrointestinal stroma tumor: Liver metastasis from partial hepatectomy

(Fig. 29.2), lymph nodes, peritoneum, and mesentery. These lesions, however, rarely present at diagnosis (Benesch et al. 2009).

29.2 Pathology/Molecular Biological Findings

Pediatric gastric GISTs are most commonly epithelioid cell tumors (Fig. 29.3) or mixed spindle and epithelioid cell tumors; whereas in adults, spindle cell tumors are the most frequent (Shimomura et al. 2010). Two genes have been implicated in the pathogenesis of GIST: *KIT* and *PDGFRA* (4q11-q12). Both genes encode for transmembrane growth factor receptors which exhibit tyrosine kinase activity. The expression of these genes

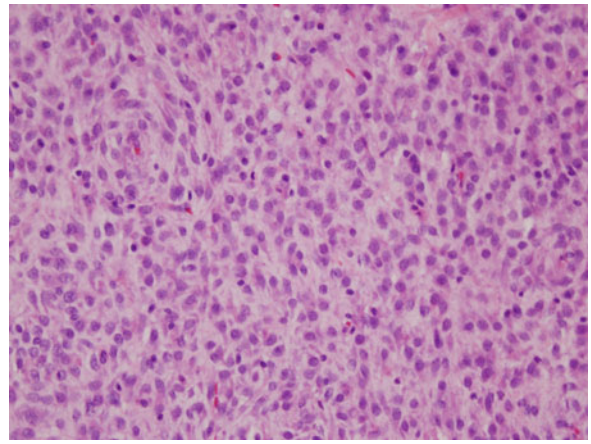

Fig. 29.3 Gastrointestinal stroma tumor: Sheets of epithelioid cells with neuroendocrine differentiation (400×)

leads to the activation of several pathways which regulate cell proliferation, adhesion, motility, and differentiation. These pathways include MEK-MAPK, STAT5, RAS, JAK2, and PI3-AKT (Liegl-Atzwanger et al. 2010; Machairas et al. 2010). Both mutations are early events in the development GIST. Researchers have found that these mutations are not involved in the malignant transformation of this tumor, only in the development and proliferation. In approximately 66% of mutated GISTs, monosomy 14 or partial loss of 14q is identified, and in approximately 50%, loss of 22q is identified. The latter is associated with the progression of GIST to a borderline or malignant lesion. Losses on chromosomes 1p, 9q, 11p, and 17q and gains on chromosomes 8q and 17q have also been identified, albeit their occurrence is rare. These mutations are also linked with malignancy. Both adult and pediatric GISTs without *KIT* or *PDGFRA* mutations display a much lower level of cytogenetic progression than mutant GISTs (Liegl-Atzwanger et al. 2010).

Expression of *KIT* is integral for the growth and preservation of cell types including germ cells, hematopoietic cells, mast cells, melanocytes, interstitial cells of Cajal, and intestinal pacemaker cells. Along with GIST, mutations in *KIT* have been identified in mast cell tumors, myelofibrosis, chronic myelogenous leukemia, and germ cell tumors. Mutations in the c-kit proto-oncogene have also been associated with the activation of the *KIT* receptor, leading to constant proliferation (Machairas et al. 2010). Mutations in *KIT* exist on exon 11 (68%), exon 9 (11%), exons 13 and 17 (0.6–4%) (Liegl-Atzwanger et al. 2010; Kaemmer et al. 2009; Machairas et al. 2010).

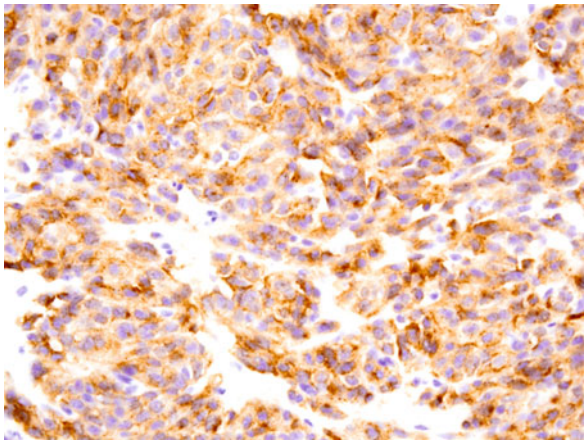

Fig. 29.4 Gastrointestinal stroma tumor: Strong positive c-kit immunohistochemical stain

When a *KIT* mutation is not indentified in GIST, typically a *PDGFRA* mutation is present (Liegl-Atzwanger et al. 2010; Kaemmer et al. 2009). *PDGFRA* mutations occur on either exon 18 or exon 14 (7%) and rarely on exon 12 (<1%). In adults, characteristics of *PDGFRA* mutated GISTs include presentation in the stomach and omentum, the appearance of epithelioid morphology, and an association with a benign clinical course (Liegl-Atzwanger et al. 2010).

No more than 10% of pediatric GIST patients display an oncogenic *KIT* mutation, and only two patients have displayed a *PDGFRA* mutation to date. The upregulation of fibroblast growth factor 4 (FGF 4), brain and acute leukemia, cytoplasmic (BAALC), insulin-like growth factor 1 (IGFR1), among others, has been reported in pediatric GIST (Benesch et al. 2009).

The immunohistochemical pattern of pediatric GIST is similar to that of adult GIST as it stains positive for CD117 (c-kit) (>95%) (Fig. 29.4); CD34 (70%); muscle markers including smooth muscle actin, calponin, and caldesmon (30%); and very rarely desmin and S100 (Benesch et al. 2009; Kaemmer et al. 2009; Machairas et al. 2010). Cytokeratins 8 and 18 are expressed in only a small percentage of GISTs while nestin, which is found in other mesenchymal tumors and schwannomas, is expressed in the majority of GISTs (Machairas et al. 2010). A road map pertaining to the diagnosis and treatment of GIST is presented in Fig. 29.5.

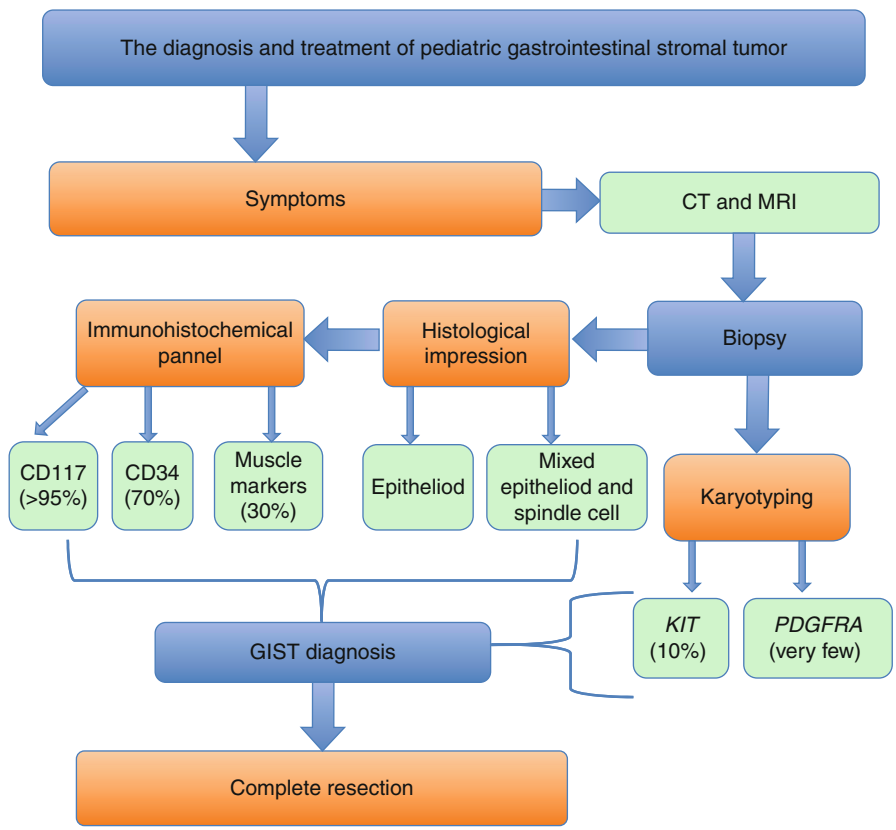

Fig. 29.5 Road map outlining the diagnosis and treatment of pediatric GIST

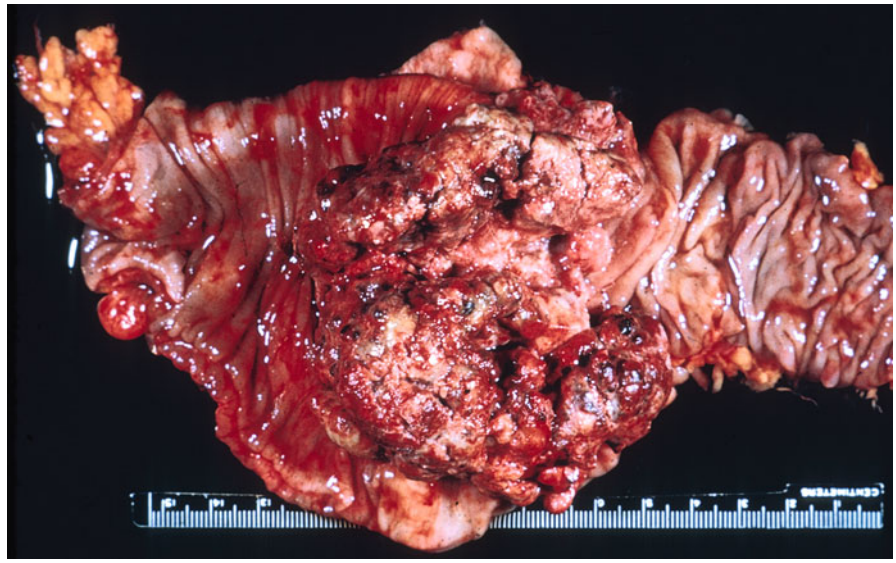

Fig. 29.6 Colon with invasive adenocarcinoma

29.3 Gastrointestinal Autonomic Nerve Tumors

Gastrointestinal autonomic nerve tumor (GANT) is a recently described variant of GIST. Required for the diagnosis of GANT is the absence of myogenic, schwann, and epithelial features (Kerr et al. 1999). They are also differentiated from GIST by showing neural differentiation using electron microscopy. While only a few cases of pediatric GANT have been reported, a slight predilection for females has been noted (Kerr et al. 1999; Benesch et al. 2009). In comparison to adult GANT, pediatric GANT tends to be smaller in size, is most commonly found in the stomach, and has a better prognosis. Pediatric GANT is typically treated using surgical resection (Kerr et al. 1999).

29.4 Colorectal Adenocarcinoma

Colorectal adenocarcinoma (CRAC) is the third most common malignancy in the adult population, surpassed by only lung and breast cancers (Sultan et al. 2010). An annual average of 9.4% of adult cancer cases and 7.9% of adult cancer deaths are attributed to CRAC, and therefore, it has been widely studied in this population. Pediatric CRAC, however, has not been extensively studied due to its rarity. Only one to two cases of CRAC per million children are reported annually (Sultan et al. 2010). The incidence of colorectal carcinoma in patients under 20 is on the rise (O'Connell et al. 2003). Sultan's investigation of the Surveillance, Epidemiology, and End Results database between 1986 and 1995 yielded 34 cases of colorectal carcinoma in patients <20 years of age; this figure nearly tripled to 94 between 1996 and 2005 (Sultan et al. 2010).

In adults, there is a slight predilection for males; however, this trend has not been reported in pediatric CRAC (Saab and Furman 2008). Patients, including those in younger age groups, typically present with abdominal pain, hematochezia, altered bowel habits, weight loss, and anemia. Pediatric patients often also complain of nausea, vomiting, abdominal distention, and abdominal mass. Acute abdominal conditions such as acute obstruction, perforation or severe pain mimicking appendicitis are also more common in children than in adults. The common occurrence of these symptoms in children may be attributed to their misdiagnosis until the mass reaches a large size. In children, the time from onset of symptoms to diagnoses is on average 3 months. This delay in diagnosis might be due to a combination of the rarity of CRAC in children and the symptomatic overlap with more common benign pediatric abdominal conditions (Saab and Furman 2008).

The pathology of CRAC is that of a malignant adenocarcinoma which often arise from polyps which undergo malignant degeneration (Fig. 29.6). In comparison to adults, where only 10–15% of tumors are

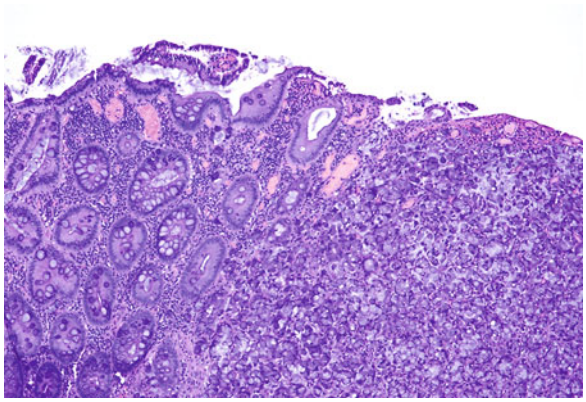

Fig. 29.7 Microscopic picture showing the transition from normal colonic mucosa to signet ring adenocarcinoma (100×)

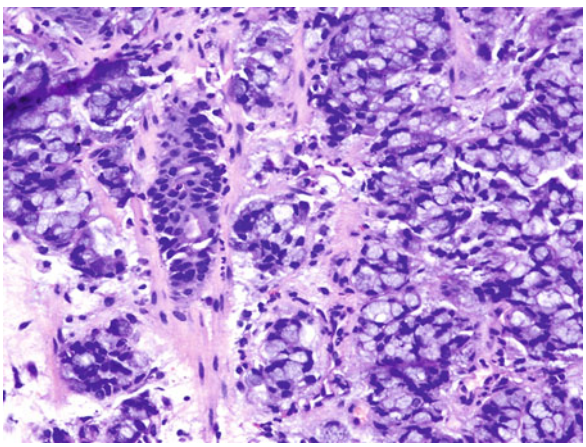

Fig. 29.8 Higher magnification of signet ring adenocarcinoma (400×)

of mucinous histology, pediatric CRACs have a high preponderance of mucinous lesions. More than 40% of tumors are signet cell carcinomas and poorly differentiated lesions (Figs. 29.7 and 29.8). The presence of this histology in adult CRAC is typically associated with an unfavorable outcome, yet due to the rarity of these tumors in children, the histological significance in this age group is unknown (Saab and Furman 2008).

A prognostic factor in adults, E-cadherin expression has not been studied in children with CRAC. Researchers have found that a decrease in E-cadherin expression in adults is an adverse prognostic indicator in several carcinomas, including esophageal, endometrial, ovarian, thyroid, and gastric (Lin et al. 2004; Mell et al. 2004; Brecelj et al. 2005; Faleiro-Rodrigues et al. 2005; Kim et al. 2009). Additionally, loss of E-cadherin is a characteristic of signet ring cell carcinoma, and it is surmised that this is an indicator for the more aggressive nature of such less differentiated colorectal carcinomas (Fig. 29.9) (Kim et al. 2002; Khoursheed et al. 2003; Borger et al. 2007). The author's current study shows no correlation between E-cadherin expression and the prognosis/staging of CRAC in children.

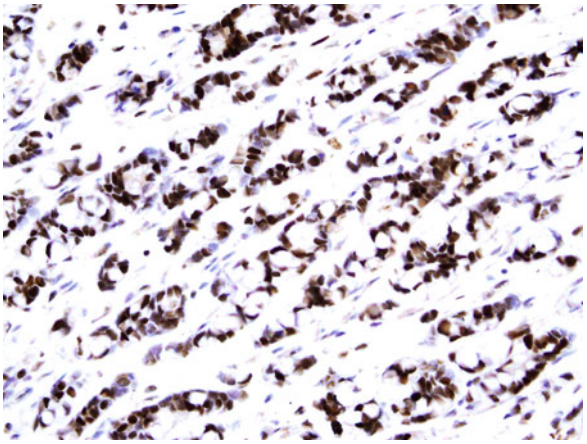

Fig. 29.9 Positive E-cadherin immunostain in signet ring adenocarcinoma

Adult CRAC staging guidelines based on surgery and pathology are typically used for children. The current staging system, developed by the American Joint Committee on Cancer, is based on the tumor pathology, lymph node involvement, margin infiltration, and occurrence of metastasis. Histologically, low-grade lesions (grade 1 and 2), which have no angiolymphatic invasion and no marginal involvement, are classified as favorable histology. If invasion is documented, total colonoscopy, complete blood count, blood chemistry panel with liver enzymes, and the carcinoembryonic antigen (CEA) level should be completed. While the CEA level in adults can help in the prediction of recurrence, the usefulness of this antigen in children remains unclear (Saab and Furman 2008). A road map pertaining to the diagnosis and treatment of CRAC is presented in Fig. 29.10.

There are three broad categories of pediatric CRAC: polyposis-associated CRAC, hereditary nonpolyposis colorectal cancer (HNPCC), and adenocarcinoma resulting from malignant degeneration of ulcerative colitis (UC). Polyposis-associated CRAC is linked with multiple familial polyposis syndromes including, familial adenomatous polyposis (FAP), MUTYH-associated

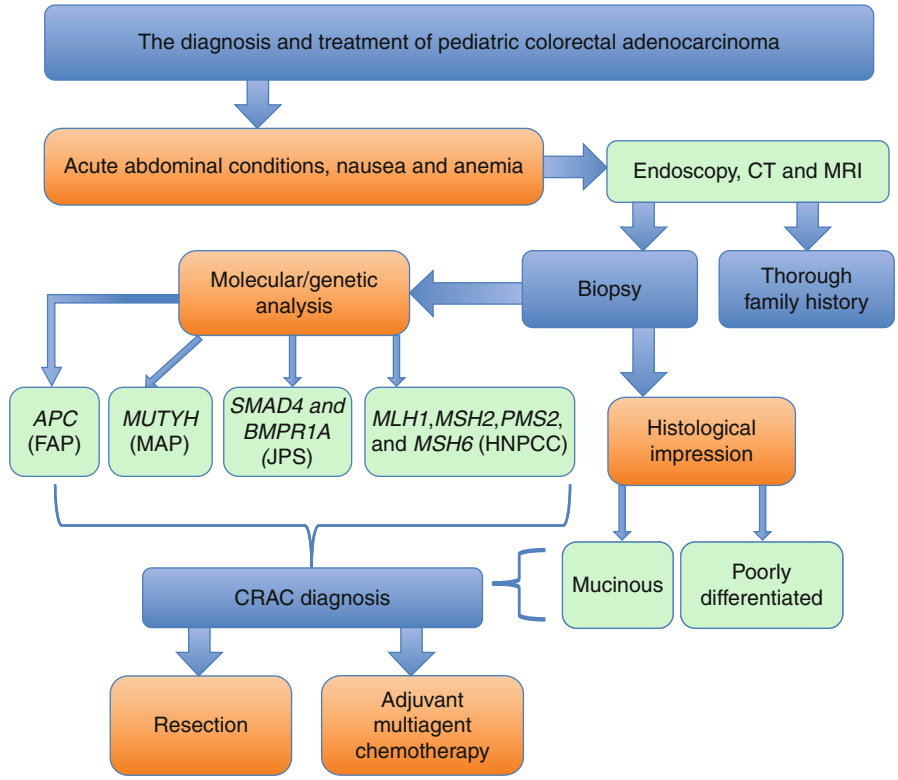

Fig. 29.10 Road map outlining the diagnosis and treatment of pediatric CRAC

polyposis syndrome (MAP), Peutz–Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), and juvenile hyerplastic polyposis syndrome (HPP) (Saab and Furman 2008). Peutz–Jeghers syndrome has not been reported in the pediatric population so it will not be further discussed.

Familial adenomatous polyposis is an autosomal dominant disorder with a 100% incidence rate of CRAC. Indicated in the etiology of this disorder is an inactivating germline mutation in 5q21, the adenomatous polyposis coli (*APC)* tumor suppressor gene. Acquired mutations of this gene are found in most sporadic cases of CRACs, and the youngest reported patient with FAB-associated CRAC was 5 years of age (Durno and Gallinger 2006; Saab and Furman 2008; Jasperson et al. 2010). MUTYH-associated polyposis syndrome, an autosomal recessive disorder, stems from a biallelic mutation in the *MUTYH* gene. According to Durno et al., only one pediatric patient (21 years of age) has had MAP-associated CRAC; however, they note that testing for this genetic mutation has not widely been performed in the pediatric population (Durno and Gallinger 2006; Jasperson et al. 2010). Juvenile polyposis syndrome is an autosomal dominant disorder with suggested germline inactivation mutations in *SMAD4* and *BMPR1A*. In patients under 35 years of age with JPS, there is a 15% incidence of CRAC (Saab and Furman 2008; Jasperson et al. 2010). Finally, the etiology of HPP is unknown (Jasperson et al. 2010).

An autosomal dominant condition, HNPCC or Lynch syndrome, accounts for roughly 3% of CRACs (Lynch, Lynch et al. 2009). Patients with Lynch syndrome have an increased risk of developing extracolonic cancers including those of the endometrium (~40%), stomach (~15%), ovary (~10%), hepatobiliary tract and pancreas (~5%), urinary tract (~4%), small bowel (~3%), and CNS (~2%) (Lagerstedt Robinson et al. 2007; Jang and Chung 2010). In comparison to patients with sporadic CRAC, those with HNPCC-related CRAC are often present at a lower stage, have lower incidence of metastases, and have more favorable prognosis (Saab and Furman 2008).

The biological basis of Lynch syndrome has been widely studied. Heterozygous germline mutations in four specific DNA mismatch repair (MMR) genes: *MLH1*, *MSH2*, *PMS2*, and *MSH6* have been linked with this disorder (5, 6). These genes are responsible for fixing sequencing errors that arise during DNA replication; therefore, if they become impaired, genetic errors may accumulate and, ultimately, carcinoma may occur. The accumulation of errors during DNA replication can occasionally lead to microsatellite instability (MSI), which is defined as erroneously lengthened or shortened repetitive DNA sequences. Most Lynch syndrome patients display MSI; however, it can also occur in up to 15% of CRACs unrelated to Lynch syndrome. In non-HNPCC patients, MSI is typically due to acquired hypermethylation of the *MLH1* gene promoter (Lagerstedt Robinson et al. 2007; Boland and Goel 2010; Jang and Chung 2010). *MLH1* and *MSH2* gene mutations are seen in up to 90% of Lynch syndrome patients while *MSH6* and *PMS2* gene mutations constitute the remaining 10% of cases (Jasperson et al. 2010). The biallelic mutations of one of the MMR genes lead to a distinct phenotype that includes multiple adenomatous polyps and café au lait skin macules (Poley et al. 2007; Durno et al. 2010).

To ensure early diagnosis of this rare disease, strict diagnostic criteria (the Amsterdam criteria) were created in 1990 with the hopes of improving morbidity and mortality rates. Since its inception, modifications have been made to include other HNPCC-related cancers (Amsterdam II criteria). The diagnostic criteria of HNPCC require the patient to have: (1) three or more family members with colorectal carcinoma where one is a first-degree relative of another, (2) two successive affected generations, and (3) the diagnosis of an HNPCC-related cancer relative before 50 years of age (Lynch et al. 2009).

Due to the rarity of CRAC in the pediatric population, routine workup should include a thorough family history and pending results, genetic testing performed (Davidson 2007; Jasperson et al. 2010). While FAP, JPS, and Peutz–Jeghers syndrome predispose patients to the formation of multiple polyps, Lynch syndrome – the most common genetic abnormalities associated with CRAC – does not, and therefore, patients with this syndrome require a higher level of clinical suspicion (Jasperson et al. 2010). If a patient is suspected of having HNPCC, genetic tests for MMR genes and immunohistochemical stains that demonstrate the absence of the protein that corresponds to the aberrant gene are available (Lynch et al. 2009). Immunohistochemical staining for microsatellite instability may also be performed in cases suspicious for HNPCC with excessive mucin or poorly differentiated signet ring cells (Jass 2007).

Behind FAP and Lynch syndrome, ulcerative colitis is the third highest condition at risk for CRAC. The development of CRAC in UC patients is mainly related to longstanding chronic inflammation of the bowel, and the longer symptoms of UC persist, the greater the chances that CRAC will occur. One study found that the presence of UC increases the risk of CRAC by 19-fold compared to the general population. When associated with UC, CRAC develops in the affected mucosa and in areas proximal to gross colitis. When UC is found in the pediatric population, the risk of CRAC is heightened (Saab and Furman 2008; Kulaylat and Dayton 2010). One report noted that children who have UC for more than 5 years are more prone to develop CRAC, whereas in the adult population, this risk does not increase until after 10 years (Saab and Furman 2008). The subtypes most often observed of UC-associated CRAC are mucinous or signet cell, and multiple lesions are typically found. Surveillance measures include regular colonoscopies as well as random serial biopsies (Kulaylat and Dayton 2010).

29.4.1 Cancer of the Stomach

Adenocarcinomas account for 95% of gastric cancers. They are extremely rare in children and adolescents (Schwartz and Sgaglione 1984). The differential diagnosis includes: GIST, lymphomas, squamous cell carcinomas, carcinoids, and leiomyosarcoma (Fig. 29.1).

29.4.2 Cancer of the Pancreas

Pancreatic cancer is a frequent cause of death from cancer in adults. Pancreatic tumors are extremely rare in children and adolescents (Dall'igna et al. 2010; Chung et al. 2006). Pancreatic cancers present variable histologies that include: papillary-cystic carcinomas, adenocarcinomas, squamous cell carcinomas, acinic cell carcinomas, liposarcomas, pancreatoblastomas, glucagonomas, gastrinomas, and malignant insulinomas (Vossen et al. 1998; Shorter et al. 2002; Raffel et al. 2004). Primitive neuroectodermal tumors and lymphomas have also

been reported (Movahedi-Lankarani et al. 2002). Many of these tumors do not produce hormones. Pancreatic carcinoma and pancreatoblastoma can produce hormones and may be associated with wasting and pain (Murakami et al. 1996; Schwartz 1997; Imamura et al. 1998). Pancreatoblastoma has been associated with Cushing syndrome and Beckwith–Wiedemann syndrome (Muguerza et al. 2005). Complete resection is the mainstay of treatment. Solid pseudopapillary neoplasm of the pancreas has been reported in children. It has been called a "borderline" malignancy. It is also treated with surgical excision. AFP elevation has also been reported in pancreatoblastoma (Dhebri et al. 2004).

29.4.3 Carcinoid Tumor

Carcinoid tumors are rare in children but may be located in the esophagus and bronchi in the thorax. In the abdomen, they occur in the pancreas and small and large bowel, including the appendix. Many are found after appendectomy. Tumors of appendix are usually benign. Tumors contain argentaffin granules which are thought to arise from small intestine Kulchitsky cells. These cells may secrete proteins, such as somatostatin, leading to the clinical symptoms of carcinoid syndrome.

29.4.4 Cancer of the Bladder, Cervix, and Vagina

Bladder carcinomas are extremely rare in children. Most pediatric bladder carcinomas are low grade, in contrast to similar tumors in adults. Papillary urothelial neoplasm of low malignant potential (PUNLUP) may be the most common entity in children (Alanee and Shukla 2010). Most of these tumors are superficial and easily treated

Table 29.1 Overview of Rare pediatric abdominal tumors

Tumor type	Adrenocortical tumors	Gastric tumors	Pancreatic tumors
Classification	• Ademona • Carcinoma	• Epithelioid leiomyoma • Leiomoyosarcoma • Carcinoid • Non-Hodgkin lymphoma	• Papillary-cystic carcinoma • Pancreatoblastoma • Acinic cell carcinoma • Malignant insulinoma • Glucagonoma • Gastrinoma • PNET • Lymphoma
Associated syndrome	• Li–Fraumeni syndrome • Beckwith–Wiedemann syndrome • Hemihypertrophy	• Epithelioid leiomyoma and leiomyosarcoma: Carney's triad	• Pancreatoblastoma: Beckwith–Weidemann syndrome and Cushing syndrome
Metastasis	• Lymph node • Kidney • Lung • Bone • Brain	N/A	• Direct invasion of liver
Treatment	• Surgical removal • Hormone therapy • Chemotherapy	• Surgical removal • Radiation therapy • Chemotherapy	• Surgical removal: partial or complete pancreatectomy • Chemotherapy
Prognosis	• Excellent: small resectable tumors • Fair: large primary tumors or metastatic disease at diagnosis	• Dependent on extent of disease and treatment success; no comprehensive studies	• Good: complete surgical resection • Poor: pancreatoblastoma

Rare tumors of the liver such as undifferentiated embryonal sarcoma are not included in this table as they are mentioned in the liver chapter

PNET primitive neuroectodermal tumor

with surgery. Squamous cell carcinomas do occur in children (Sung and Koyle 2000; Lezama-del Valle et al. 2004). In pediatric cancer survivors, there is an association between the development of bladder carcinoma and treatment with alkylating agents, such as cyclophosphamide (Johansson and Cohen 1997). Adenocarcinoma of cervix and vagina are extremely rare in children and adolescents (McNall et al. 2004). The median age of presentation is 15 years, and two-thirds are associated with exposure to diethylstilbestrol in utero. These tumors tend to present at higher stage III or IV in these adolescents. This may be because this population is not routinely examined with routine PAP smears.

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