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Abdominal neoplastic manifestations of neurofibromatosis type 1

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Abstract

Neurofibromatosis type 1 (NF1) is an autosomal dominant hereditary tumor syndrome, with a wide clinicopathologic spectrum. It is defined by characteristic central nervous system, cutaneous and osseous manifestations, and by mutations in the NF1 gene, which is involved in proliferation via p21, RAS, and MAP kinase pathways. Up to 25% of NF1 patients develop intra-abdominal neoplastic manifestations including neurogenic (commonly plexiform neurofibromas and malignant peripheral nerve sheath tumors), interstitial cells of Cajal (hyperplasia, gastrointestinal stromal tumors), neuroendocrine, and embryonal tumors (rhabdomyosarcoma). Nonspecific symptoms, multifocal disease, or coexistence of 2 or more tumor types make patients challenging to diagnose and manage. Screening for intra-abdominal tumors in NF1 patients remains controversial, and currently no guidelines are established. Management decisions are complex and often informed by single-center experiences or case studies in the literature, though the field is rapidly evolving. Thus, NF1 patients should be followed in specialist centers familiar with their wide spectrum of pathology and with multidisciplinary care including specialized pathology and radiology. This review will (1) provide a contemporaneous synthesis of the literature and our multi-institutional clinical experiences with intra-abdominal neoplasms in NF1 patients, (2) present a classification framework for this heterogeneous group of disorders, and (3) outline approaches to screening, surveillance, diagnosis, and management.

Keywords

gastrointestinal stromal tumor | malignant peripheral nerve sheath tumor | neoplasms | neurofibromatosis type 1 | plexiform neurofibroma

Neurofibromatosis type 1 (NF1) is an autosomal dominant hereditary tumor syndrome, caused by loss of function mutations or losses in the *NF1* gene located on chromosome 17q11.2. Neurofibromin, the cytoplasmic protein product of this gene, controls cellular proliferation through the p21, RAS, and MAP kinase pathways and is expressed in multiple tissues, resulting in a wide spectrum of clinical findings.[1] The incidence of *NF1* is approximately 1 in 2500–3000, making it one of the most common hereditary multitumor syndromes. The gene has a high mutation rate, and only around a half of *NF1* mutations are familial, with the remainder occurring de novo, primarily in paternally derived chromosomes. Penetrance is complete; however, expression of *NF1* is highly variable, depending on the type of mutation (nonsense, frameshift or splice mutations, or deletions are the most common), the time at which the mutation occurs, and the presence of molecular alterations in associated genes,[1] resulting in a heterogeneous group of associated clinical manifestations. The major disease features of NF1 involve the CNS, skin, and bone. NF1 carries a 60% lifetime risk of developing a malignancy, especially of the nervous system.[2] Benign tumors,

particularly neurofibromas, are very common in NF1 patients, and some such as plexiform neurofibromas (PNs) are essentially pathognomonic. The diagnosis of NF1 is primarily clinical and uses criteria developed initially in 1987 by the NIH Consensus Conference, later updated in 1997, based on the presence of at least 2 characteristic clinical features (Table 1).[3] These clinical criteria are both highly sensitive and specific and are considered more useful as an initial tool for identifying NF1 than mutation analysis. Owing to the large size of the NF1 gene, and the heterogeneity of mutations, molecular testing is complex and requires sequencing all of the coding exons, and testing for deletions or rearrangements of the entire gene, especially for de novo cases. Around 5% of patients who meet the clinical criteria for NF1 will not have an identifiable mutation on sequencing.

In addition to characteristic CNS, cutaneous and osseous manifestations of NF1, between 5% and 25% of patients will develop intra-abdominal (gastrointestinal or retroperitoneal) neoplastic manifestations. These typically develop later in life, with the exception of intra-abdominal PN and rhabdomyosarcoma (RMS). Intra-abdominal neoplasms may be benign or malignant; however, even benign disease can pose serious complications related to tumor mass effects within the abdomen. Collectively, they represent a challenging subgroup of clinical conditions to diagnose, screen, and manage and not infrequently manifest as multifocal disease.

This review summarizes the existing literature on intra-abdominal neoplasms in the NF1 population, presents a classification framework for considering this heterogeneous group of disorders in the NF1 patient (Table 2), and outlines clinical approaches for diagnosis and management, screening, and surveillance.

Table 1 Diagnostic Criteria of Neurofibromatosis Type 1 (NF1)[3]

Diagnostic Criteria of NF1
Two or more criteria are required for diagnosis
Six or more café au lait macules (>0.5 cm in children or >1.5 cm in adults)
Two or more cutaneous or subcutaneous neurofibromas or one plexiform neurofibroma
Axillary or inguinal freckling
Optic pathway glioma
Two or more Lisch nodules (iris hamartomas on slit-lamp examination)
Bony dysplasia (sphenoid wing dysplasia, bowing of long bone ± pseudoarthrosis)
One first-degree relative with NF-1

Table 2 Classification of Abdominal Neoplasms Associated With NF1

Reported Intra-abdominal Neoplastic Manifestations of NF1
Neurogenic neoplasms
Solitary neurofibroma
Plexiform neurofibroma
Diffuse mucosal/submucosal neurofibromatosis
Ganglioneuromatosis
Malignant peripheral nerve sheath tumor
Interstitial cells of Cajal lesions
Gastrointestinal stromal tumors (GISTs)
Multifocal
Solitary
Minute incidental GISTs tumorlets
Interstitial cells of Cajal hyperplasia
Neuroendocrine tumors
Pheochromocytoma
Neuroendocrine neoplasms
Somatostatinoma
Embryonal
Rhabdomyosarcoma
Miscellaneous
Adenocarcinoma at different GI sites, vasculopathy
Juvenile-like mucosal GI polyps

Diagnosis and Management

A heterogeneous group of intra-abdominal neoplasms, both benign and malignant, are associated with NF1. These can be classified according to their cellular origin as neurogenic neoplasms, interstitial cells of Cajal neoplasms, neuroendocrine neoplasms (NENs), and embryonal neoplasms (Table 2). Diagnosis and management strategies depend on the type of intra-abdominal tumor, but in general, timely and detailed radiologic assessment, expert pathology review, and discussion in a multidisciplinary setting with NF1 expertise are required. Decision-making for NF1 patients with abdominal tumors is complex, rapidly evolving, and often informed only by relatively small, single-center experiences in the published literature. A summary of diagnostic and management approaches to the most common intra-abdominal neoplasms seen in NF1 is presented in Table 3.

Neurogenic Tumors

The most common peripheral nerve sheath tumors in patients with NF1 are neurofibromas. These are benign tumors comprised of a mixture of Schwann cells, fibroblasts, perineural cells, and mast cells, though it is the Schwann cell that is the primary tumor cell. Neurofibromas may appear as focal growths or extend along nerves, involving multiple fascicles, where they are defined as PNs. PNs are highly specific for NF1. They originate from the neural plexus and are often multiple.[4] They occasionally have the potential for malignant transformation into malignant peripheral nerve sheath tumors (MPNST), a soft tissue sarcoma that is typically high grade, with a propensity for distant metastasis.[5] Peripheral nerve sheath tumors, particularly PN, occur relatively infrequently in the gastrointestinal tract.[1]

Table 3 Overview of Clinical Evaluation and Management of Common NF1-Associated Abdominal Neoplasms

	Common Sites	Investigations	Pathology	Management	Surveillance
Neurogenic neoplasms					
Plexiform neuroma	Small bowel; retroperitoneum	MRI ^{18}F-FDG-PET/CT to evaluate the malignant transformation	High-risk features for malignant transformation: -Atypia AND: -Loss of neurofibroma architecture, -High cellularity -High mitotic activity (>1/50 but <3/10 hpf)	Surgical: excision if symptomatic and anatomically accessible Medical: promising results with MEK inhibition to reduce tumor volume	At least annual clinical history/exam. MRI FDG-PET if concern for malignant transformation based on hx/exam or MRI
MPNST	Paraspinal, retroperitoneal. GI sites uncommon	CT, MRI	High-grade soft tissue sarcoma	Multidisciplinary evaluation: 1. Surgical: en bloc resection of tumor, surrounding structures with the goal of R0 resection 2. Radiation: consideration of neoadjuvant RTX 3. Medical Oncology Consultation	CT and/or MRI every 3–4 months for the first 2–3 years, then every 6 months until 5 years
Interstitial cells of Cajal lesions					
GIST	Small bowel >> gastric Often multifocal	CT abdomen/pelvis ±CT enterography	KIT/PDGFRA mutation negative; SDH competent	Primary resectable GIST: for small (<3 cm), low-risk lesions surveillance may be appropriate, surgical resection for higher risk lesions, or those increasing in size with negative histological margins Adjuvant: typically imatinib-resistant as KIT/PDGFRA (–)	CT abdomen/pelvis every 3–6 months for 1–5 years, then annually thereafter. For nonoperative approach: if the mass remains stable over time, the interval between imaging can be increased
Neuroendocrine tumors					
Pheochromocytoma	Adrenal, typically solitary and unilateral	1. Labs: 24h urinary catecholamines and metanephrines, plasma-free metanephrines 2. Imaging: adrenal CT, MRI. If malignant pheochromocytoma suspected: staging with CT C/A/P, bone scan MIBG	Histologically and immunophenotypically identical to non-NF1 pheochromocytoma	*Require preoperative alpha-blockade Benign disease: laparoscopic adrenalectomy Malignant disease: resect primary and metastatic disease, usually larger lesions may require an open approach Adjuvant (for malignant disease): radiation for bulky primary tumors, I-131 MIBG if tumor takes up MIBG, chemotherapy considered in rapidly growing/unresectable tumors	BP check, plasma/urinary metanephrines every 3–12 months. CT imaging annually can be considered
Neuroendocrine neoplasms **Somatostatinoma**	Ampulla of Vater, periampullary duodenum	1. Labs: Serum CgA, 24 h urinary HIAA 2. Imaging: CT abdomen/pelvis Somatostatin-receptor scintigraphy, EUS if considering endoscopic resection	Stain diffusely positive for somatostatin, tubular and glandular architectural pattern predominates, few mitotic figures	1. Surgical: Consider endoscopic resection if: <2 cm, confined to mucosa/submucosa on EUS, no lymphadenopathy OR Segmental resection, avoid resection with pancreaticoduodenectomy if possible	1. Labs: CgA/5HIAA every 3–6 months for the first year, then every 6–12 months 2. Imaging: CT C/A/P every 6–12 months If abnormal, octreotide scan or MIBG
Embryonal tumors					
Rhabdomyosarcoma*	Any site	PET/CT	Predominantly embryonal subtype	Chemotherapy, radiation	None

*Seen exclusively in pediatric (<18 years) NF1 patients.

Plexiform Neurofibromas

PN may be congenital or acquired and increase most rapidly in size during childhood.[6] However, in one series, which used whole-body MRI imaging in a cohort of NF1 patients, intra-abdominal PNs were most commonly seen over the age of 40 years, and a majority were asymptomatic.[7] In the abdomen, they are reported to affect predominantly the small bowel, retroperitoneum, and less frequently, the colon.[8] It is uncommon for them to involve liver and bile ducts, but they can involve the periportal spaces and liver hilum, often associated with extensive abdominal and retroperitoneal involvement.[9] Symptoms, if they do occur, can be nonspecific and relate to tumor mass effect (pain especially along the distribution of a nerve, palpable abdominal mass, GI tract, or biliary obstruction) or bleeding if there is mucosal involvement.[1,4]

Patients who develop symptoms from PNs should be urgently referred to a specialist center for multidisciplinary input including specialist imaging and pathology review. This is especially important given the potential for malignant transformation into MPNST. CT and MRI are the initial imaging modalities of choice. It is difficult to predict which PNs are at risk for malignant transformation although the rapid expansion of the PN and/or pain (high sensitivity, low specificity) or new neurological deficit (moderately high specificity, low sensitivity) are notable to watch for.[10]

Retroperitoneal PNs often arise from the paraspinal spaces as symmetric, bilateral lesions.[8] Mesenteric PNs often appear as multiple discrete nodules or infiltrating lesions extending from the root of the mesentery to the wall of the intestine.[11] Percutaneous biopsy of lesions worrisome for malignant transformation should be performed along with expert pathologic assessment.

Imaging and Pathology

PNs on MRI are isointense to muscle on T1-weighted images, demonstrate a target sign on fluid sensitive sequences, and demonstrate variable enhancement, but typically demonstrate no early arterial enhancement.[12] A target sign is seen as a high signal intensity periphery due to myxoid paucicellular and central intermediate-to-dark signal intensity due to cellular areas.[13]

MRI findings can be useful at identifying higher risk radiologic features ominous for MPNST including tumor depth below the fascia (highly sensitive, but not specific), presence of necrosis more than 25%, and tumor size (>5 cm).[14] Ill-defined or infiltrative margins, perilesional edema, absent target sign, and early arterial enhancement have also been reported for MPNST.[12] Utilization of MRI diffuse-weighted sequences has demonstrated significantly lower diffusivity in MPNST compared to benign PN (likely correlating to higher cellularity in cases of malignancy on pathology).[15] In the same study, the authors looked at morphological criteria and reported that peritumoral edema was the most common feature seen in MPNST.

Fluorodeoxyglucose (^{18}F-FDG)-PET/CT differentiates between benign neurofibromas and MPNSTs with high sensitivity (>90%) and very good specificity (~71–84%).[14,16–18] A literature review of PET/CT in the evaluation of MPNST reported a significant difference between the mean SUV between benign and malignant lesions (1.93 vs 7.49); however, there was a significant overlap between the SUV_{max} of benign and malignant lesions making differentiation difficult.[19] Reported SUV_{max} for PN versus MPNST is 1.85 ± 1.03 and 3.84 ± 3.98, respectively, in one series.[20] A tumor-to-liver (TTL) ratio has also been proposed for malignant differentiation, with PN 1.23 ± 0.61 versus MPNST 3.2 ± 2.7. At our institution, we generally use a SUV_{max} of 3.5 cutoff as a threshold for elevating suspicion for MPNST. A TTL ratio of more than 2.6 has been suggested as a cutoff for raising suspicion.[12] Biopsy of several sites within a PN may be required to evaluate for malignant transformation. Several histological features of PN on biopsy have been proposed as portending to a higher risk of transformation (expert consensus).[21] Nuclear atypia in the absence of other concerning histological features is generally not significant. Loss of neurofibroma architecture, high cellularity, and/or mitotic activity (>1/50 but <3/10 hpf) should raise suspicion for malignancy. Neurofibromas with at least 2 of these features on biopsy are considered "atypical neurofibromatous neoplasms of uncertain biologic potential," and additional sampling, clinical correlation, and expert pathology review are recommended.[21]

Management

Surgical management of symptomatic or rapidly enlarging PNs has traditionally been advocated where technically feasible to manage pain, bleeding, obstruction, and symptoms of mass effect and should be considered as a strategy in cases when malignant transformation potential is very concerning. However, PNs are often difficult tumors to resect because they may involve an entire nerve plexus and as they emanate from the spinal cord. Although they may appear as well-defined masses clinically and radiologically, they frequently invade adjacent soft tissue, and therefore even where resection is possible, local recurrences are not uncommon. Thus, experts who have experience with managing NF1 patients should perform these procedures. Specifically, preoperative biopsies targeting the areas of most concern for malignant transformation should be performed along with correlation to serial imaging to optimize surgical planning and to avoid piecemeal resection of possible sarcoma. For tumors in technically challenging locations, such as the porta hepatis, nonoperative management with surveillance imaging has been reported in small series to be safer than resection, with a very low risk of malignant transformation.[9]

Prior to transformation, PNs are benign and do not respond to traditional chemotherapy agents. Recently, new small molecule selective inhibitors of mitogen-activated protein kinase (MEK1/2) have demonstrated efficacy in reducing tumor volume and associated mass effect symptoms associated with PN in pediatric patients.[22,23] In 2019 selumetinib, one of the MEK inhibitors, was granted breakthrough therapy designation by the FDA to expedite its development for use in the clinical setting.[24] There is limited data on the efficacy and safety of MEK inhibitors for the treatment of PNs in adult NF1 patients.

Malignant Peripheral Nerve Sheath Tumor

Among individuals with NF1, there is an 8–13% lifetime risk of developing an MPNST, and this remains the leading cause of death in NF1 patients. MPNST comprises 10% of all malignant sarcoma in adults, and approximately half of all MPNSTs occur in the setting of NF1.[10] The paraspinal region, head, and neck are the most common locations for MPNST in NF1: intra-abdominal MPNSTs are rare and often clinically silent until late in the disease process.

Patients presenting with retroperitoneal or abdominal lesions concerning for MPNST require cross-sectional imaging with CT and/or MRI. Because necrosis is often present within the tumor, a heterogenous enhancement pattern is often seen. The tumor borders are often irregular and infiltrative with evidence of invasion into adjacent organs.[25] As previously discussed, FDG-PET/CT may be useful for differentiating between PN and MPNST.[19]

Histological diagnosis is typically performed using a combination of light microscopy and immunohistochemistry (IHC) and requires expert pathology review. Definitive histological diagnosis can be challenging, as the morphological features are nonspecific and an IHC marker is lacking.[26] Complete loss of H3K27me3 is an IHC marker with diagnostic potential in high-grade MPNST, though it may be most useful in radiation-induced MPNST rather than NF1-associated MPNST.[27] In general, like most soft tissue sarcomas, the need for a surgical biopsy is limited with the safety of interventional radiology guided biopsy using coaxial needles.[28,29] If a surgical biopsy is required, care should be taken not to violate fascial planes, and this should not compromise definitive resection.

MPNSTs are high-grade soft tissue sarcomas and have a high propensity for distant metastasis (especially lung). All patients with MPNST should be managed in expert centers with the input of a multidisciplinary Sarcoma team. Surgical resection remains the mainstay of treatment, yet this is often a challenge since often these tumors involve large neural plexuses and R0 resections maybe consequently morbid. Even with negative surgical margins, local and distance recurrences are common. As with extremity soft tissue sarcoma, preoperative or postoperative radiation may be used with the goal of reducing the risk of local recurrence, though there is conflicting data and no prospective studies evaluating this question in the setting of MPNST.[30] Chemotherapy may be used as neoadjuvant therapy to facilitate resection in otherwise borderline or unresectable cases.[31]

Tumor size and margin status appear to be the most important prognostic factors associated with survival in NF1-associated MPNST.[32,33] Only one retrospective series with more than 100 patients in it has shown NF1-MPNST (vs sporadic MPNST) as an adverse prognostic factor in cancer-specific survival on multivariate analysis.[34] Lower survival in NF1-associated MPNST compared to sporadic MPNST in smaller studies and on univariate analysis may in part explained by differences in tumor location, size, and positive margin rate.[31,32,35] To date, there are no identifiable distinct molecular differences between NF1-associated and sporadic MPNSTs to suggest different underlying tumor biology; however, this is being actively researched with next-generation sequencing and methylation profiling.[35]

Interstitial Cells of Cajal Lesions: Gastrointestinal Stromal Tumors

Interstitial cells of Cajal lesions in NF-1 span hyperplasia, to minute incidental gastrointestinal stromal tumors (GIST tumorlets), to solitary and multifocal GIST. NF1-associated GIST comprises less than 1% of all GIST; however, GIST is the most common gastrointestinal tumor reported in the NF1 population.[36] In a study of 70 Swedish adults with NF1 (mean age 44 years), 7% developed GIST over a 12-year period of clinical surveillance.[37] In another series, 25% of NF1 patients were found to have a GIST at autopsy.[38]

The clinicopathologic profile, mutational status, and prognosis of patients with NF1-associated GIST were characterized in a pooled cohort of 126 NF1 patients with 252 GIST.[36,39] The majority (52.5%) were clinically asymptomatic and discovered incidentally, compared to approximately 19% of sporadic GIST in a comparable population. NF1-associated GISTs occur most frequently in the small bowel (duodenum 19.8%, jejunum 39.2%, and ileum 30.6%) compared to stomach (5.4%), occur in more than 1 gastrointestinal site (multifocality), and are associated with a median age of diagnosis 10 years earlier than sporadic GIST. NF1-associated GISTs are characterized by small tumor size and low mitotic activity, with 64.9% being classified as low risk using Miettinen's risk classification system,[40] and in the presence of these features, often follow an indolent clinical course.[39] Interstitial cells of Cajal hyperplasia are also commonly seen in resection specimens for NF1-associated GIST possibly as a precursor lesion, and minute GIST tumorlets can also occur.[1]

The molecular signature of NF1-associated GIST is distinct from sporadic tumors as they rarely harbor *KIT* or *PDGFRA* mutations; the tumor however uniformly stain positive for *KIT* by IHC.[39] This suggests that mutations of *KIT* and *PDGFRA* are not implicated in the tumorigenesis of NF1-associated GIST.[41] Recently, MAX mutations have been uncovered in 50% of NF1-syndromic GISTs, which is thought to disrupt cell cycle regulation and occur early in tumorigenesis.[42] Mutations in succinate dehydrogenase (SDH) enzyme which are commonly seen in other "wild-type" GIST are also not found in NF1-associated tumors (NF1-associated GISTs are SDH-competent).[43] Nonetheless, molecular analysis is still recommended in all patients found to have NF1-associated GIST to rule out the presence of an imatinib-sensitive mutation. The presence of multiple small bowel GISTs that are *KIT/PDGFRA* mutation negative should raise suspicion for NF1 in patients without a prior diagnosis.

The indolent biological behavior of NF1-associated GIST warrants a modified approach to surveillance. For example, an examination of the GI tract can be considered to document the extent of multifocality which may be under-represented on routine cross-sectional imaging studies. Traditional tyrosine kinase inhibitors such as imatinib are not effective in wild-type GIST, and thus, surveillance frequency can be tailored to patient symptoms. For example, indication for surgery maybe for a tumor that is associated with GI symptoms or pain, rather than slow growth on sequential scans.

The risk of recurrence and cancer-specific mortality appears to be very similar between NF1 and non-NF1 patients after surgical resection of GISTs; however, this data is limited.[44] New therapeutic targets are also being identified as more is understood about the tumorigenesis of NF1-associated GIST.

Neuroendocrine Tumors

Pheochromocytoma

Pheochromocytomas are catecholamine producing tumors that arise from the enterochromaffin cells of the adrenal medulla and can be benign or malignant and are associated with cancer predisposition syndromes, including NF1, in almost 25% of cases.[45] They occur in 1–7% of all NF1 patients, and in 20–50% of all adult NF1 patients with hypertension.[45] Most adults with NF1 who develop a pheochromocytoma have tumor-related symptoms including hypertension, headache, palpitations, and/or diaphoresis.[46] NF1-associated lesions are solitary and unilateral in 84% of patients and extra-adrenal in a location in only a small minority (~6.1%).[45]

Work up and imaging features for pheochromocytomas are similar for NF1 and non-NF1 patients and include 24 h urine for catecholamines and metanephrines, plasma-free metanephrines, CT, or MRI. Adrenal CT washout or MRI with opposed-phase T1-weighted sequences can be useful for distinguishing adrenal pheochromocytoma from benign adenoma. As with all pheochromocytomas, an alpha-adrenergic blockade is needed preoperatively, followed by postoperative beta blockage as necessary for rebound tachycardia. The benign disease can often be removed laparoscopically, though tissue handling should be minimized intraoperatively to mitigate the catecholamine surge and close communication with the anesthesia team maintained throughout. As pheochromocytomas can occur in NF1 alongside other, sometimes more easily diagnosed conditions, NF1 patients have developed cardiovascular crises while undergoing anesthesia for another indication, because of an unknown pheochromocytoma.[47] The possibility of concomitant pheochromocytoma in hypertensive patients with NF1 who have surgery planned for other indication/s should be considered (as discussed for GIST), and where necessary preoperative evaluation with urinary catecholamines undertaken. Chemotherapy is used in unresectable tumors and radiation for bulky tumors, with neither of these specific to NF1.

Gastrointestinal Neuroendocrine Neoplasms

Gastrointestinal NENs are more common in NF1 than in the general population and show a predilection for the peri-ampullary duodenum or near the ampulla of Vater. They show a similar rate of malignancy as in the general population. NF1-associated NENs are typically well-differentiated, with favorable tumor biology. In one larger series of 74 cases of NF1-associated periampullary tumors, somatostatinomas were the most common tumor type, responsible for 40% of cases.[48] Somatostatinomas in NF1 stain strongly for somatostatin on IHC, but typically do not present with the "classic" clinical symptoms of diarrhea, diabetes, dyspepsia, and cholelithiasis. Instead, they may be clinically silent, or present with obstructive jaundice, duodenal obstruction, pancreatitis, or cholangitis.[1,49] Diagnosis relies on CT, endoscopic ultrasound (EUS), and measurement of chromogranin A (CgA) and urinary 5-HIAA.[50] Management does not differ from that of non-NF1 NENs. For well-differentiated ampullary NENs of more than 2 cm and for poorly differentiated ampullary neuroendocrine carcinomas, pancreaticoduodenectomy is usually required in patients who are surgical candidates. Local tumor excision is preferred over pancreaticoduodenectomy for periampullary NENs less than 2 cm depending on their relation to the ampulla. Endoscopic resection is an option if less than 2 cm and confined to mucosa/submucosa on EUS. In patients amenable to curative resection, good medium-term outcomes are reported, with 75% alive at a median of 30 months post-resection.[48]

GISTs and Neuroendocrine Tumors in NF1

GISTs can co-exist with NENs in NF1. Somatostatinoma and GIST are almost pathognomonic, and GIST can coexist with pheochromocytoma and NENs in the NF1 patient. At least 14 cases where both GIST and pheochromocytoma occurred in NF1 patients have been reported in the literature,[11,51] all pheochromocytomas were adrenal in location (Figure 1). Thus, it is prudent to screen for the presence of a pheochromocytoma prior to surgical management of GISTs in NF1 patients, as anesthesia can exacerbate the life-threatening cardiovascular effects of catecholamines, and carries a high risk of perioperative mortality in patients with undiagnosed pheochromocytoma. Only 2 cases of an MPNST co-occurring with a GIST in an NF1 patient have been reported.[52,53]

Embryonal Tumors

Rhabdomyosarcoma

RMS is the most common soft tissue sarcoma in children and is also associated with NF1, where it occurs exclusively in pediatric patients. In pediatric RMS cohort studies, 0.5–1% of RMS cases are associated with NF1.[54,55] NF1-associated RMS typically have an earlier age of onset than the general population (usually under 3 years age) and are almost exclusively of the embryonal histotype. Overall, embryonal RMS generally has a better prognosis than alveolar histotype. Treatment of RMS has evolved significantly over the past two decades, with the adoption of risk-adapted therapy based on clinicopathologic prognostic factors, and the use of multi-modal treatment consisting of chemotherapy, surgery where feasible, and/or radiotherapy. These improvements have been driven by cohort studies and clinical trials from international cooperative groups, namely, the Intergroup Rhabdomyosarcoma Study Group.[56] Patients

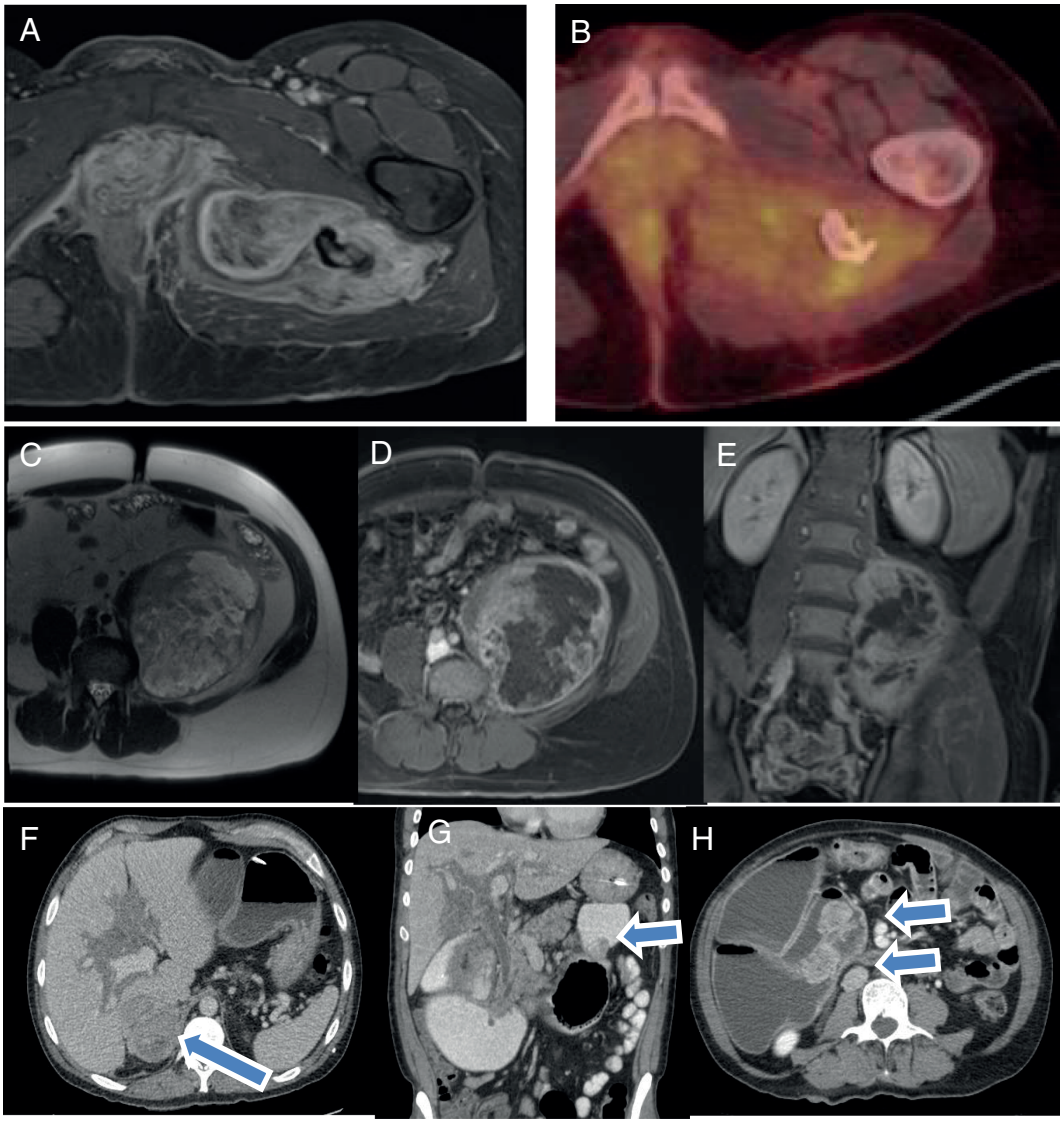

Figure 1. Imaging characteristics of abdominal neoplasms in NF1 patients. Axial postcontrast T1-weighted fat-saturated MR image demonstrates an infiltrative enhancing plexiform neurofibroma in the proximal left obturator region with components extending into the perineum and pelvic floor (A). Axial fused PET/CT image of the plexiform neurofibroma demonstrates low levels of FDG uptake with SUV_{max} 3.6–3.8; however, no definite areas for were suspicious for malignant transformation (B). Axial T2-weighted MR image demonstrates a heterogeneous mixed solid and cystic mass in the left retroperitoneum arising from the left L3 nerve root. Core biopsy was performed and pathology was consistent with malignant peripheral nerve sheath tumor (MPNST) (C). Axial and coronal postcontrast T1-weighted fat-saturated images demonstrate heterogeneous enhancement of the periphery and soft tissue components of the MPNST (D and E). Axial postcontrast CT image demonstrates a heterogeneous right adrenal mass in keeping with pheochromocytoma. There is also infiltrating low-attenuation soft tissue around the imaged portal structures (F). Coronal postcontrast CT image further demonstrates the infiltrating periportal soft tissue mass, in keeping with a plexiform neurofibroma. There is also patulous distension of the duodenum with oral contrast. In the proximal jejunum, there is a soft tissue mass in keeping with gastrointestinal stromal tumor (GIST) which was subsequently resected (G). Axial postcontrast CT image demonstrates routine surveillance of further intraluminal masses in the distended proximal duodenum, in keeping with further GISTs (H).

with NF1-associated RMS are treated similarly to those with sporadic disease, with no reported differences in outcome.

Role of Screening and Surveillance for Intra-abdominal Neoplasms in NF1 Patients

NF1 is associated with reduced life expectancy, reported to be between 8 and 15 years below that of the general population.[46,57] Premature death is primarily attributed to the development of malignant neoplasms, particularly MPNSTs. In a study of US death certificates, people with NF1 were 34 times more likely to have a malignant connective or other soft tissue neoplasm listed on their death certificate compared to those without the condition.[46]

Vigilant longitudinal care of NF1 patients is important for the early detection and management of associated

intra-abdominal neoplasms.[3] Annual clinical examination by clinicians familiar with the wide spectrum of NF1-associated disease, and ideally in the multidisciplinary setting of highly specialized centers, remains the recommended approach for early detection of both NF1 complications and neoplastic transformation.[1,58] Physicians not familiar with NF1 may not associate intra-abdominal neoplasms with the syndrome, as they are less common and not part of the diagnostic criteria. Whole-body or site-specific screening for neoplasm in NF1 is not currently recommended by guideline groups, except by some in the setting of optic pathway glioma in the pediatric population.[59] In asymptomatic patients, many centers monitor PN with targeted MRI. Symptomatic patients should have directed imaging with MRI and/or PET/CT. Routine screening with whole-body MRI with diffusion-weighted imaging can also be performed for patients who are deemed high risk (ie, NF1 gene microdeletion, family or personal history of atypical neurofibroma or MPNST, prior radiation therapy, or high internal PN burden).[12] In a case series of 152 patients with NF1 followed between 1988 and 1992, ad hoc (physician discretion) screening for intra-abdominal manifestations, using abdominal ultrasound and urinary catecholamine levels, did not offer any benefit in terms of earlier diagnosis compared to annual clinical examination, with investigations offered only for concerning history and physical exam findings.[58] However, imaging modalities have improved substantially since then, and this question needs to be reevaluated in the modern era of CT, MRI, and/or PET. An analogous hereditary syndrome with a high propensity to develop multiple cancer types that has been definitively shown to benefit from a screening approach is Li-Fraumeni Syndrome. Here, long-term compliance with a comprehensive surveillance protocol (which included biochemical tumor markers, whole-body MRI, brain MRI, breast MRI mammography, abdominopelvic ultrasound, and colonoscopy) for early tumor detection was associated with improved long-term survival.[60] Based on the frequency of neoplasms in the NF1 population, similar screening approaches may reduce the premature cancer-related mortality associated with the condition; however, this approach is not yet proven.

PN should be monitored closely in NF1, because of their potential for malignant transformation, and patients should be encouraged to present promptly if they notice changes in growth or pain associated with these lesions. Malignant transformation occurs most commonly from the time of adolescence through mid-adulthood, and patients and their families should be educated about the risk of developing MPNST.[61] In symptomatic patients, prompt investigation with MRI and/or 18FDG-PET should be undertaken along with appropriate specialist referral. Many intra-abdominal PNs are clinically silent, yet still harbor a risk of malignant transformation. Screening for malignant transformation with MRI or 18FDG-PET for MPNST has been suggested by some, on the basis that survival after MPNST in NF1 patients is associated with tumor volume,[16,34] but this is not currently considered a routine standard of care. At our center, we offer 18FDG-PET for NF1 patients with PNs who have any change in size or consistency of their tumor on palpation, new pain, or changes on MRI that are concerning. Furthermore, we are able to use 18FDG-PET to guide biopsy to areas of highest FDG uptake (SUV) in order to acquire the tissue at most risk.

Conclusions and Future Directions

Intra-abdominal neoplasms are an under-recognized entity among NF1 patients, despite their relatively frequent occurrence. They can also represent first presentations of the syndrome, and tumor multifocality, or the co-existence of 2 different tumor types (eg, GIST and neuroendocrine tumors) should raise the possibility of NF1. Hereditary multitumor syndromes are best managed in specialized centers with a multidisciplinary approach to care across the life course. We strongly advocate the adoption of this approach for NF1 patients as well. Diagnosis of NF1-associated intra-abdominal neoplasms can be complex, particularly given the nonspecific nature of symptoms, but vigilance is required, and patients should also be counseled to present early if they experience new symptoms. In patients with known PNs, the potential for malignant transformation should be at the forefront of the clinician's mind, as MPNSTs remain the leading cause of premature mortality in NF1 patients. Whole-body screening for malignancy or malignant transformation in NF1 is not currently recommended. As our understanding of the molecular mechanisms driving tumorigenesis in NF1 grows, new therapeutic targets are appearing on the horizon. The early success of MEK inhibition in reducing tumor volume in children with PN, and its relatively rapid translation into clinical practice, speak to the potential to improve outcomes for NF1 patients, and reduce tumor-related morbidity and mortality. Similar studies are needed in adults. While surgical resection remains the mainstay of curative-intent treatment for malignant intrabdominal neoplasms in NF1, judicious use of nonoperative surveillance approaches for benign tumors, particularly in anatomically challenging locations, may reduce treatment-related morbidity. Finally, the literature on NF1-associated intra-abdominal neoplasms is dominated by case reports and small, single-institution case series. A better understanding of the epidemiology, natural history, and outcomes for these patients, as well as delivery of clinical trials, could be achieved through collaborative international initiatives, similar to those that have transformed the treatment of pediatric RMS.

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