

Signs and Symptoms of Childhood Cancer: A Guide for Early Recognition

IOANNA FRAGKANDREA, MD, PhD, *The Royal Marsden Hospital, Sutton, London, United Kingdom*

JOHN ALEXANDER NIXON, MD, *Epsom and St. Helier NHS University Hospital, Sutton, London, United Kingdom*

PARASKEVI PANAGOPOULOU, MD, MPH, PhD, *Panagiotis and Aglaia Kyriakou Children's Hospital, Athens, Greece*

Although cancer in children is rare, it is the second most common cause of childhood mortality in developed countries. It often presents with nonspecific symptoms similar to those of benign conditions, leading to delays in the diagnosis and initiation of appropriate treatment. Primary care physicians should have a raised index of suspicion and explore the possibility of cancer in children who have worrisome or persisting signs and symptoms. Red flag signs for leukemia or lymphoma include unexplained and protracted pallor, malaise, fever, anorexia, weight loss, lymphadenopathy, hemorrhagic diathesis, and hepatosplenomegaly. New onset or persistent morning headaches associated with vomiting, neurologic symptoms, or back pain should raise concern for tumors of the central nervous system. Palpable masses in the abdomen or soft tissues, and persistent bone pain that awakens the child are red flags for abdominal, soft tissue, and bone tumors. Leukokoria is a red flag for retinoblastoma. Endocrine symptoms such as growth arrest, diabetes insipidus, and precocious or delayed puberty may be signs of endocranial or germ cell tumors. Paraneoplastic manifestations such as opsoclonus-myoclonus syndrome, rheumatic symptoms, or hypertension are rare and may be related to neuroblastoma, leukemia, or Wilms tumor, respectively. Increased suspicion is also warranted for conditions associated with a higher risk of childhood cancer, including immunodeficiency syndromes and previous malignancies, as well as with certain genetic conditions and familial cancer syndromes such as Down syndrome, Li-Fraumeni syndrome, hemihypertrophy, neurofibromatosis, and retinoblastoma. (*Am Fam Physician*. 2013;88(3):185-192. Copyright © 2013 American Academy of Family Physicians.)

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The annual incidence of cancer in children who live in developed countries is between 105 and 150 cases per 1 million children,¹ making it the second leading cause of childhood mortality after injury.² The distribution of the various types of childhood cancer is shown in *Table 1*.²⁻⁶ To avoid missing the early diagnosis of childhood malignancies, primary care physicians should have a high index of suspicion along with excellent physical examination skills.

In studies of children with malignant tumors, the median delay in diagnosis was nine weeks for brain tumors, three weeks for leukemia, and 11.6 weeks for solid tumors.^{7,8} The parental delay in seeking care was considerably shorter than the physician delay in making the diagnosis,⁹ emphasizing that parents are usually the best observers of their children, and that physicians should listen to the parents' concerns. In this review, we present common and less common early presenting signs and symptoms of childhood

cancer, with an emphasis on red flag symptoms that should prompt evaluation.

Initial Assessment and Clinical Examination

Cancer diagnosis in children is often delayed because the presenting symptoms tend to be nonspecific and resemble those of benign conditions. In children who exhibit red flag symptoms for malignancy, a complete history, including personal and family history, is fundamental. Preliminary symptoms may have started abruptly (e.g., bone pain after minor trauma) or developed insidiously over a few weeks to several months (e.g., intermittent headaches). They may also be constitutional and nonspecific (e.g., fatigue, pallor, fever, anorexia) or localized (e.g., a palpable mass). A focused physical examination, including funduscopy, should follow.

Symptoms suggestive of specific malignancies in adults (such as rectal bleeding, which could indicate colon cancer, or breast lumps, which are suggestive of breast cancer)

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
Any combination of persistent or unexplained fever, recurrent or persistent infection, pallor, malaise, hemorrhagic manifestations, hepatosplenomegaly, or lymphadenopathy should be evaluated with CBC and blood smear.	C	10-12
Enlarged lymph nodes—especially those larger than 2 cm that persist for more than four to six weeks or that are associated with fever, night sweats, weight loss, hepatosplenomegaly, or orthopnea—should be evaluated with CBC, blood smear, erythrocyte sedimentation rate, and chest radiography.	C	10, 12, 14
Headaches of new onset and with certain features (persistent, occipital, awakening the child or occurring in the morning, associated with nausea and vomiting or neurologic deficits) may indicate a brain tumor when other causes such as migraine, sinusitis, tension headache, and ocular abnormalities are excluded. Taking a history and performing a neurologic examination are essential before neuroimaging is requested.	C	12, 19, 28
Any abdominal mass or hepatosplenomegaly, especially if associated with anorexia, vomiting, fever, or pain, or in a child who appears ill, requires further evaluation with ultrasonography.	C	5, 12
Bone pain that persists, awakens the child, does not respond to nonsteroidal anti-inflammatory drugs, or is associated with swelling should be evaluated with two-view radiography, C-reactive protein measurement, CBC, and blood smear.	C	12, 22, 23
Persistent back pain that appeared recently in a child younger than four years requires further investigation with CBC, blood smear, C-reactive protein measurement, and radiography of the spine.	C	12, 19
Any palpable, recent, nontender soft tissue mass, especially if larger than 2 cm, should be examined with ultrasonography or magnetic resonance imaging.	C	12

CBC = complete blood count.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort>.

are rare in childhood, in which leukemia, brain tumors, and lymphoma account for more than 67% of all neoplasms.² The typical clinical characteristics of childhood cancer appear in *Table 1*.²⁻⁶ Symptoms that should raise suspicion for cancer are discussed below.

Clinical Red Flags for Malignancy

Most red flags (e.g., fever, lymphadenopathy, vomiting, pallor) are also present in common and benign ailments and rarely result from a malignancy. It is important to interpret the red flag finding in combination with other findings from the history and physical examination, especially if the patient presents repeatedly with the same symptom or if the symptom persists. The most common nonspecific signs and symptoms associated with an underlying malignancy are listed in *Table 2*.^{4-6,10-25}

CONSTITUTIONAL SYMPTOMS

Prolonged fever with no identifiable cause is a common symptom of cancer in children, and is associated mainly with leukemia or lymphoma.¹¹ Symptoms such as pallor, fatigue, malaise, and reduced level of activity that are not associated with an acute infection may be caused by several types of cancer. Anorexia is common in many childhood illnesses. It could indicate a malignant cause if it persists, cannot be explained, results in failure to thrive or weight loss (defined as 10% loss of body weight in six months), or is associated with other suspicious findings.^{4,13} “B symptoms” are the combination of prolonged

drenching night sweats, fever, and significant weight loss; together with lymphadenitis, they are typical of Hodgkin lymphoma.⁴ Hemorrhagic diathesis (characterized by petechiae, ecchymoses, recurrent epistaxis, and bleeding gums) merits further investigation because it may indicate that malignant cells have infiltrated the bone marrow. The differential diagnosis includes idiopathic thrombocytopenic purpura, clotting factor deficiencies, and platelet dysfunction. In conclusion, any combination of persistent or unexplained fever, recurrent or persistent infection, pallor, malaise, hemorrhagic manifestations, hepatosplenomegaly, or lymphadenopathy should be evaluated with complete blood count and blood smear.¹⁰⁻¹²

LYMPHADENOPATHY

Localized or generalized lymphadenopathy is a common complaint in children. Most cases of lymphadenopathy are benign and related to infections or collagen vascular diseases.¹⁴ Initial management (depending on the location) involves watchful waiting for up to four weeks; other options include a 10-day course of oral antibiotics (although evidence to support this practice is lacking and should be reserved for patients who show evidence of local inflammation).^{12,26,27} If lymphadenopathy persists or other symptoms such as fever, night sweats, weight loss, hepatosplenomegaly, or orthopnea exist, malignancy should be excluded, and evaluation with complete blood count, blood smear, erythrocyte

Table 1. The Most Common Types of Childhood Cancer and Their Main Clinical Characteristics

<i>Malignancy</i>	<i>Frequency (%)^{2,3}</i>	<i>Main clinical characteristics⁴⁻⁶</i>
Leukemia (acute lymphoblastic leukemia; acute myelogenous leukemia)	34.1	Pallor, fatigue, prolonged fever with no identifiable cause, persistent or recurrent infections, anorexia, petechiae, bruising or gingival bleeding, lymphadenopathy, hepatosplenomegaly, bone pain (generalized or involving the joints) or limp, irritability, neurologic symptoms
Central nervous system tumors (brain, cranial nerves, spinal cord)	22.6	Persistent headache (mainly in the morning), nausea and vomiting, ataxia, visual disturbances (diplopia, squint, papilledema, proptosis), neurologic deficits (cranial nerve palsies, motor and sensory signs), seizures, developmental delay or regression, unexplained deteriorating school performance, personality changes, torticollis, signs of raised intracranial pressure (increasing head circumference, bulging fontanelle, irritability)
Lymphoma (Hodgkin, non-Hodgkin)	11.5	Lymphadenopathy, fever or "B symptoms" (night sweats, fever, weight loss), pallor, fatigue, petechiae or bruising, abdominal mass, hepatosplenomegaly, nausea and vomiting, constipation, abdominal pain
Neuroblastoma	7.6	Palpable mass (abdomen, neck), anorexia and failure to thrive, fever, bone pain, lymphadenopathy, pallor, malaise, irritability, leg weakness, ocular symptoms (periorbital ecchymoses, proptosis, squint, opsoclonus-myoclonus syndrome, heterochromia of the iris, Horner syndrome), back pain, subcutaneous nodules, obstructive symptoms of the bowel and bladder, neurologic deficits
Soft tissue sarcomas (mainly rhabdomyosarcoma)	6.1	Palpable mass, symptoms caused by pressure on adjacent structures, lymphadenopathy (depending on location of tumor), squint or proptosis (orbital location), vaginal bleeding (vaginal location)
Renal tumors (mainly Wilms tumor)	5.6	Abdominal mass, abdominal pain, hematuria, vomiting, constipation, fever, hypertension
Germ cell tumors	3.1	Palpable mass (scrotum), respiratory symptoms (mediastinal location), abdominal distension and pain (abdominal location), constipation, enuresis, precocious puberty or amenorrhea, vaginal bleeding, leg weakness, neurologic symptoms (central nervous system location)
Osteosarcoma	2.3	Localized bone pain, palpable mass, swelling or deformity, pathological fracture
Ewing sarcoma	2.1	Localized bone pain, palpable mass (depending on location), prolonged fever, fatigue, weight loss, compression of local structures (bladder, spinal cord), symptoms due to bone marrow infiltration
Retinoblastoma	2.1	Leukokoria (cat's eye reflex), squinting, vision loss
Hepatic tumors	1.1	Abdominal distention or mass, symptoms depend on type of tumor
Histiocytosis	< 0.5	Bone pain (localized or generalized), rashes (eczema resistant to treatment), fever, weight loss, lymphadenopathy, hepatosplenomegaly, chronic ear discharge or otitis media, proptosis, diabetes insipidus
Nasopharyngeal carcinoma	< 0.5	Cervical lymphadenopathy, persistent nasal obstruction, epistaxis, persistent otitis media, tinnitus, headache, fever, trismus, dysphagia, cranial nerve palsies
Others	< 1	Clinical characteristics depend on location and histology (various malignant epithelial carcinomas [e.g., thyroid, lung, breast, bladder, skin], melanomas, or unspecified neoplasms)

NOTE: Symptoms are listed in order of importance and frequency of appearance. Information from references 2 through 6.

sedimentation rate, and chest radiography is needed.^{10,12,14} Enlarged supraclavicular and epitrochlear lymph nodes have a higher risk of malignancy than other sites.¹⁴ The most common malignant causes of lymphadenopathy are shown in *Table 2*.^{4-6,10-25}

NEUROLOGIC SYMPTOMS

Neurologic symptoms occur in many malignancies and are present in 88% of patients with central nervous system tumors at diagnosis.^{15,16} In children younger than two years, common neurologic symptoms are nonspecific and include unexplained irritability or lethargy, developmental delay or regression, and increasing head

circumference. Headaches are also reported by 40% to 50% of elementary school-aged children and by 60% to 80% of high school-aged children.¹⁷ Headaches should be considered suspicious if they have started recently; occur in the morning or at night and awaken the child (46% to 76% of central nervous system tumors present with morning headaches); and are accompanied by vomiting.^{15,16,18} Occipital location is also suspicious.¹⁹

A neurologic examination and funduscopy should be performed to help distinguish a brain tumor from conditions such as migraine, sinusitis, tension headache, and ocular abnormalities. Abnormalities of gait (ataxia) and coordination increase suspicion for brain tumor,

Table 2. Clinical Red Flags Associated with Childhood Malignancies

<i>Signs and symptoms</i>	<i>Suspicious clinical characteristics</i>
Pallor, fatigue, malaise	Especially if persistent and associated with signs of bone marrow infiltration (unexplained fever, recurrent infections, hemorrhagic diathesis) and/or lymphadenopathy ¹⁰⁻¹²
Fever	Prolonged (> 2 weeks) with no identifiable cause; associated with weight loss, night sweats, pallor, petechiae, mass, bone pain, lymphadenopathy
Recurrent or treatment-resistant infections	May be associated with pallor, petechiae, weight loss, bone pain, lymphadenopathy, hepatosplenomegaly, or a palpable mass
Anorexia and weight loss	Protracted, unexplained anorexia, especially if accompanied by significant weight loss or other suspicious findings (recurrent infections, fever, pallor, lymphadenopathy, hepatosplenomegaly)
Lymphadenopathy	
Localized	Persistent or progressive that does not resolve after 4 to 6 weeks or that does not respond to antibiotic treatment; lymph nodes > 2 cm, firm, nontender; supraclavicular and epitrochlear location
Generalized or localized	Coexisting fever, night sweats, weight loss, malaise, pallor, hepatosplenomegaly
Hemorrhagic manifestations (petechiae, ecchymoses, recurrent epistaxis, bleeding gums)	Persistent and combined with other signs of bone marrow infiltration (pallor, fatigue, recurrent infections)
Headaches	Of new onset, persistent, occur in the morning or awaken the child from sleep; without history of migraine; associated with vomiting or neurologic deficits (cranial nerve palsies, motor and sensory signs); occipital location; worse when lying down
School performance deterioration; personality and mood changes	Of recent onset, progressive, and not otherwise explained
Palpable abdominal mass	Any mass discovered outside the neonatal period has high probability of malignancy, especially when associated with vomiting, abdominal pain, constipation, hematuria, or hypertension
Hepatosplenomegaly	Should always be investigated even if no associated symptoms are found
Vomiting	Persistent and recurring; associated with morning headaches; associated with abdominal mass
Bone pain, joint pain/arthritis Limp or refusal to walk	Bone pain that awakens the child at night, lasts > 2 weeks, is localized, is associated with swelling, and does not improve with nonsteroidal anti-inflammatory drugs
Back pain, kyphoscoliosis, lordosis, torticollis	Back pain of sudden onset; age < 4 years; worse at night; accompanied by fever or neurologic abnormalities; not associated with trauma; not relieved by nonsteroidal anti-inflammatory drugs
Masses or lumps on extremities, head, neck, trunk	Any palpable mass that appeared recently; is located deep in the fascia; is nontender, hard, and > 2 cm in diameter; or is associated with regional lymphadenopathy
Urine retention/enuresis	Of recent origin, associated with neurologic deficits or abdominal masses
Scrotal swelling or mass	Of recent origin Isolated right-sided varicocele
Gingival swelling/bleeding	Not otherwise explained
Dermatologic manifestations	"Eczema" not responding to conventional treatment Subcutaneous nodules

NOTE: Symptoms are listed in order of how often they are encountered in malignancies and on their clinical importance (i.e., how specific the symptom is for the diagnosis of the respective malignancy). Tumors are presented in order from most common to least.

Information from references 4 through 6, and 10 through 25.

especially of the posterior fossa.¹⁶ Seizures are the initial presentation in approximately 10% of central nervous system tumors.¹⁵ Seizures that are focal, without fever or a history of epilepsy or trauma, or that are associated with other neurologic symptoms or signs warrant

investigation with neuroimaging.¹⁵ Neurologic deficits (e.g., cranial nerve palsies, motor and sensory problems such as leg weakness) can be the presenting features of several malignant conditions such as leukemia, neuroblastoma, and lymphoma, and occasionally Ewing

Suggested malignancies

Leukemia, lymphoma, neuroblastoma, Ewing sarcoma, histiocytosis

Leukemia, lymphoma, neuroblastoma, Ewing sarcoma, Wilms tumor, histiocytosis, nasopharyngeal carcinoma

Leukemia, lymphoma, neuroblastoma, rhabdomyosarcoma, Ewing sarcoma

Leukemia, lymphoma, central nervous system tumors, abdominal tumors

Lymphoma, rhabdomyosarcoma, nasopharyngeal carcinoma

Lymphoma, leukemia, neuroblastoma

Leukemia, lymphoma, neuroblastoma, Ewing sarcoma

Brain tumor, neuroblastoma, leukemia, lymphoma, nasopharyngeal carcinoma

Brain tumor

Neuroblastoma, nephroblastoma, lymphoma, hepatic tumors, ovarian tumors

Leukemia, lymphoma, hepatic tumors

Brain tumors, abdominal tumors (neuroblastoma, Wilms tumor, lymphoma, hepatoblastoma)

Osteosarcoma, Ewing sarcoma, leukemia, neuroblastoma, histiocytosis
Same as the above, and central nervous system tumors

Spinal cord/brain tumors, neuroblastoma, leukemia

Soft tissue sarcoma

Neuroblastoma, tumors of the spinal cord or pelvis (ovarian, soft tissue sarcoma)

Germ cell tumors, leukemia, soft tissue sarcoma

Renal tumor, lymphoma, sarcoma

Histiocytosis, leukemia

Histiocytosis

Neuroblastoma, leukemia, histiocytosis

sarcoma, rhabdomyosarcoma, and nasopharyngeal carcinoma.²⁰ Unexplained deteriorating school performance and personality changes may also be caused by brain tumors.^{12,19,28} It is important to balance concerns about malignancy with appropriate caution regarding

overuse of computed tomography, because imaging exposes children to significant doses of radiation, increasing their long-term risk of malignancy.

GASTROINTESTINAL SYMPTOMS

Any abdominal mass should be treated with a high degree of suspicion. In neonates, abdominal masses are usually of benign genitourinary origin.²¹ In children younger than five years, the most common malignant causes are neuroblastoma and nephroblastoma. The differential diagnosis also includes cysts and benign tumors of the kidneys, ovaries, or soft tissues. Abdominal masses, as well as any degree of hepatosplenomegaly, call for further investigation with ultrasonography, especially if they are associated with anorexia, vomiting, fever, pain, or a child who appears ill.^{5,12} Persistent vomiting also requires further investigation, especially if it accompanies headaches or neurologic deficits and occurs mainly in the morning.¹⁵

Recent onset constipation that persists and does not respond to conservative treatment should be evaluated for abdominal masses that may cause bowel obstruction or spinal cord lesions that affect sphincters.^{5,6} In children older than six years with intussusception, abdominal lymphoma must be ruled out.⁴ Diarrhea may be a symptom of leukemia or lymphoma, but when it is intractable and watery, it may be caused by a vasoactive intestinal-peptide–secreting neuroblastoma.⁴

MUSCULOSKELETAL SYMPTOMS

Bone pain that occurs at night, awakens the child, and is persistent or intermittent can be a first sign of malignancy. Localized pain associated with swelling or deformity may indicate a bone tumor.²² Before attributing the symptom to benign causes (e.g., “growing pains”)²³ or recent trauma,⁴ the examining physician should evaluate the patient with two-view radiography of the specific site, C-reactive protein measurement, complete blood count, and blood smear.^{12,22,23}

Generalized bone pain may indicate leukemia or neuroblastoma.¹⁹ Joint pain or arthritis usually ascribed to rheumatoid disorders (especially if accompanied by fever or rash) may also be caused by leukemia,¹⁹ whereas disruption of normal gait or refusal to walk can be caused by pain or reduced motor function associated with several malignancies.²⁴ Back pain, lordosis, kyphoscoliosis, and torticollis of sudden onset are rare symptoms of cancer. Back pain merits further investigation with CBC, blood smear, C-reactive protein level, and two-view radiography of the spine if the child is younger than four years, if the pain worsens at

Table 3. Endocrine Symptoms and Associated Childhood Malignancies

<i>Symptom</i>	<i>Associated malignancy</i>
Diabetes insipidus	Craniopharyngioma, germinoma, histiocytosis, suprasellar tumors of the pituitary gland
Growth arrest	Craniopharyngioma, germinoma, suprasellar tumors of the pituitary gland or the hypothalamus
Precocious puberty	Adrenal tumors, central nervous system tumors, human chorionic gonadotropin–secreting germ cell tumors, rhabdomyosarcoma
Pubertal delay	Pituitary tumors

Information from references 25, and 30 through 32.

Table 4. Paraneoplastic Symptoms and Syndromes Associated with Childhood Malignancies

<i>Paraneoplastic symptom/syndrome</i>	<i>Description</i>	<i>Associated malignancy</i>
Catecholamine hypersecretion–related symptoms	Attacks of sweating, flushing, hypertension, pallor, palpitations	Neuroblastoma
Hypercalcemia	—	Leukemia, Wilms tumor
Hypertension, erythrocytosis, Cushing syndrome, acquired von Willebrand disease	—	Wilms tumor
Intractable watery diarrhea	Caused by hypersecretion of vasoactive intestinal peptide	Neuroblastoma
Opsoclonus-myoclonus syndrome (“dancing eyes–dancing feet”)	Bursts of rapid, chaotic eye movements with frequent, involuntary, irregular, jerking muscle movements	Neuroblastoma
Osteoporosis	—	Hepatoblastoma
Rheumatic symptoms	Musculoskeletal pains, fever, fatigue, arthritis, weight loss, hepatomegaly, back pain	Leukemia, neuroblastoma, lymphoma, Ewing sarcoma, central nervous system tumors

NOTE: Malignancies are listed in order from most common to least. Information from references 4, 33, and 34.

GENITOURINARY SYMPTOMS

Hematuria is a frequent finding in urinary tract infections, trauma, or lithiasis. If common causes have been excluded, renal tumor or soft tissue sarcoma should be considered. Urine retention or enuresis of recent origin may result from spinal or pelvic tumors.⁴ Vaginal bleeding in prepubertal girls may be associated with vaginal rhabdomyosarcoma⁶ or with a hormone–secreting germ cell tumor. Every scrotal mass should be investigated, because it may be caused by a soft tissue or germ cell tumor, or even leukemia.⁶ Finally, an isolated right-sided varicocele is a red flag for a right kidney or other tumor and priapism of leukemia.

CARDIORESPIRATORY SYMPTOMS

Rarely, cardiorespiratory symptoms may be associated with malignancy. Nonproductive cough, dyspnea, or orthopnea with no obvious cause that persists for more than two to three weeks and does not respond to treatment, or that is associated with other disturbing findings (lymphadenopathy, weight loss, fever, pallor, facial swelling or plethora) may result from a mediastinal mass or a pleural effusion caused by lymphoma or leukemia.¹⁹ Hypertension is rare in children, and may be associated with Wilms tumor, neuroblastoma, and pheochromocytoma.

EAR, NOSE, AND THROAT SYMPTOMS

Gingival swelling or bleeding may result from gum infiltration in leukemia or histiocytosis.^{6,19} Chronic otorrhea may be caused by middle ear histiocytosis, rhabdomyosarcoma, or nasopharyngeal carcinoma.^{6,19} Nasal obstruction, epistaxis, and dysphagia may be signs of nasopharyngeal carcinoma or other tumors of the area.¹³

DERMATOLOGIC SYMPTOMS

Dermatologic manifestations provide information on bone marrow function through clinical signs such as pallor and bruising or petechiae. Additionally, subcutaneous nodules with bluish (“blueberry muffin”) or normal skin appearance may be caused by leukemia, neuroblastoma, or histiocytosis.²⁵ Pruritus is a rare manifestation of Hodgkin lymphoma.⁴ A scaly, seborrheic, eczematoid rash involving the scalp, ear canals, abdomen, and

night, or if there are concurrent symptoms.^{12,16,19} Pathologic fractures occurring at areas of osteolytic lesions may be caused not only by osteoporosis or cerebral palsy, but also by malignancies such as osteosarcoma, Ewing sarcoma, or histiocytosis.¹⁹ Finally, any palpable mass of the soft tissues that has recently appeared on the extremities, head, neck, or trunk warrants further investigation with ultrasonography or magnetic resonance imaging.¹²

Table 5. Medical Conditions and Syndromes Associated with Increased Risk of Childhood Cancer

Condition or syndrome	Main associated malignancies
Childhood cancer survivors (exposure to alkylating agents and radiotherapy, stem cell transplant recipients)	Acute myelogenous leukemia, brain tumor, non-Hodgkin lymphoma, myelodysplastic syndromes
Conditions with DNA damage repair defects (ataxia-telangiectasia, Bloom syndrome, Fanconi anemia)	Leukemia; lymphoma; myelodysplasia; Wilms tumor; hepatocellular carcinoma; stomach, colon, or breast carcinoma
Denys-Drash syndrome	Wilms tumor
Down syndrome	Acute lymphoblastic leukemia, acute myelogenous leukemia
Familial retinoblastoma (parent or sibling)	Retinoblastoma, osteosarcoma
Gastrointestinal syndromes (familial adenomatous polyposis, Gardner syndrome)	Colon and other gastrointestinal cancers, hepatoblastoma, medulloblastoma
Hemihypertrophy syndromes (Beckwith-Wiedemann syndrome)	Hepatoblastoma, Wilms tumor
Immunodeficiency disorders (Wiskott-Aldrich syndrome, common and severe combined immunodeficiency)	Leukemia, non-Hodgkin lymphoma
Li-Fraumeni syndrome (autosomal dominant condition associated with a germline p53 mutation, familial appearance)	Adrenal and brain tumors and soft tissue sarcomas before 10 years of age, bone sarcomas in adolescents
Neurocutaneous syndromes (neurofibromatosis, tuberous sclerosis, von Hippel-Lindau disease)	Optic and other glioma, brain tumor, neurofibrosarcoma, peripheral nerve sheath tumor, leukemia, Wilms tumor
Turner syndrome	Gonadoblastoma
WAGR syndrome	Wilms tumor
Xeroderma pigmentosum	Melanoma, skin carcinoma

NOTE: Malignancies are presented in order from most common to least.

WAGR = Wilms tumor, aniridia, genitourinary abnormalities or gonadoblastoma, and mental retardation.

Information from references 36 and 37.

intertriginous areas of the neck and face that does not respond to treatment with topical corticosteroids may be a sign of histiocytosis.⁶

OCULAR SYMPTOMS

Several ocular symptoms warrant immediate attention because malignancy should be excluded before other diagnoses are considered. Squinting and diplopia are red flags for tumors of the eye and brain. Leukokoria (cat's eye reflex) is a red flag for retinoblastoma. Proptosis is a red flag for space-occupying lesions of the orbit (rhabdomyosarcoma, leukemia, optic glioma, histiocytosis). Neuroblastoma may manifest with periorbital ecchymoses ("raccoon eyes") and, rarely, opsoclonus-myoclonus syndrome, Horner syndrome,²⁹ or acquired heterochromia of the iris. Aniridia may be associated with Wilms tumor.⁴

ENDOCRINE SYMPTOMS

The most common endocrine symptoms associated with childhood malignancies are described in *Table 3*.^{25,30-32} They include diabetes insipidus (polyuria, polydipsia), growth arrest, precocious puberty, and pubertal delay. They may be caused by endocranial tumors (causing hypopituitarism) or by hormone-secreting germ cell tumors.^{31,32} Concomitant headaches or visual disturbances should alert the physician.¹³ Diencephalic syndrome is a rare cause of failure to thrive in early childhood associated with neoplasms of the hypothalamic–optic chiasmatic region.^{4,6}

Paraneoplastic Syndromes and Symptoms

Paraneoplastic syndromes and symptoms are more common in adults than in children.³³ The most common paraneoplastic syndromes and symptoms associated with childhood malignancies are shown in *Table 4*.^{4,33,34} and are most often caused by neuroblastoma⁴ or Wilms tumor.³³ Rare paraneoplastic manifestations include osteoporosis and symptoms suggestive of rheumatic diseases.³⁴

Medical Conditions and Syndromes Associated with Childhood Cancer

Certain conditions predispose children to the development of cancer. These include genetically inherited disorders and syndromes, immunodeficiency disorders, and familial cancer syndromes. Siblings of children with a malignancy (especially twins) and survivors of childhood cancer are also at increased risk.³⁵ The most common conditions and syndromes associated with increased likelihood of a childhood malignancy are presented in *Table 5*.^{36,37}

Data Sources: We searched PubMed, the Cochrane Database of Systematic Reviews, Essential Evidence Plus, Clinical Evidence, the National Guideline Clearinghouse, the Institute for Clinical Systems Improvement, UpToDate, and the National Institute for Health and Clinical Excellence. Google Scholar was used to access full-text articles when not available through the publisher's site. Key words included childhood cancer or pediatric malignancies, and early diagnosis or delayed diagnosis or suspected cancer in children or symptoms or signs. A subsequent search was performed to identify usual and unusual presentations of specific types of cancer (e.g., neuroblastoma, leukemia). The identified articles were read initially by title, the relative abstracts were read in full, and then searches were done for the full articles. Certain pediatric oncology textbooks also were used to confirm that all aspects of the subject were adequately covered. Search dates: May 2011 and December 2011.

The Authors

IOANNA FRAGKANDREA, MD, PhD, is a clinical oncologist in the Neuro-oncology Unit at The Royal Marsden Hospital, Sutton, London, United Kingdom.

JOHN ALEXANDER NIXON, MD, is a clinical fellow at Epsom and St. Helier NHS University Hospital, Sutton, London, United Kingdom. At the time this article was written, he was a resident in orthopedic surgery at Frimley Park Hospital, Frimley, Surrey, United Kingdom.

PARASKEVI PANAGOPOULOU, MD, MPH, PhD, is an attending physician in the Department of Pediatric Hematology-Oncology at Panagiotis and Aglaia Kyriakou Children's Hospital in Athens, Greece.

Address correspondence to Paraskevi Panagopoulou, MD, MPH, PhD, Panagiotis and Aglaia Kyriakou Children's Hospital, Levadias 2, Athens, Greece 11527 (e-mail: vivianpa@otenet.gr). Reprints are not available from the authors.

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