How to suspect cancer in Primary Care

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Abstract

Cancer in childhood has a low incidence and its clinical presentation is often nonspecific simulating common pathologies of benign course, therefore making its diagnosis highly challenging. The main symptoms and signs of suspected childhood cancer in Primary Care are: pallor, masses (in the head, neck and other locations), lymphadenopathy, abnormal movement, bruising and signs of bleeding, fatigue, headache, visual abnormalities, pain and musculoskeletal symptoms. The Primary Care pediatrician must recognize when an apparently benign symptomatology may be the beginning of a severe pathology, identifying those warning signs that require immediate assessment. A detailed medical history, a complete physical examination and a clinical follow-up are essential. The objective is to reduce the time from the onset of symptoms to the final diagnosis, so as to allow an early diagnosis of childhood cancer.

Resumen

El cáncer en la infancia presenta baja incidencia, su presentación clínica con frecuencia es inespecífica y simula patologías comunes de curso benigno, lo que dificulta su diagnóstico. Los principales síntomas y signos de sospecha de cáncer en Atención Primaria son: palidez, masas (en cabeza, cuello y otras localizaciones), adenopatías, movimientos anormales, hematomas y signos de sangrado, fatiga, cefalea, anormalidades visuales, dolor y síntomas musculoesqueléticos. El pediatra de Atención Primaria ha de reconocer cuándo una sintomatología aparentemente benigna puede ser el inicio de una patología grave, identificando aquellos signos de alarma que requieren estudio inmediato. Son necesarias una buena historia clínica, una exploración física completa y un seguimiento clínico evolutivo. El objetivo es disminuir el tiempo desde el inicio de los síntomas hasta el diagnóstico final, de tal forma que permita un diagnóstico precoz de cáncer infantil.

Key words: *Infant; Child; Neoplasms; Primary health care; Early detection of cancer.*

Palabras clave: Lactante; Niño; Neoplasias; Atención Primaria; Diagnóstico precoz de cáncer.

Introduction

Childhood cancer has a low incidence and often manifests nonspecifically, simulating other frequent and benign processes. These particularities make it difficult to diagnose cancer in Primary Care. However, an early suspicion, together with a rapid referral of the patient to a specialized center, may have implications at the prognostic and therapeutic level, as well as in the emotional impact secondary to the diagnosis on the patient and his family.

Epidemiology

Childhood cancer is after accidents, the second leading cause of death beyond the first year of life.

The standardized annual incidence of childhood cancer in Spain is 159 new cases per year per million children aged 0 to 14 years, which represents 1,100 new cases of childhood cancer per year, an incidence similar to that of the rest of Europe[1]. It is estimated that a Primary Care pediatrician following 1,500 patients in his clinic, will see a new case of cancer every 5 years. Overall 5-year survival after the diagnosis is around 79%[1]. Despite recent advances, childhood cancer is the second leading cause of death from the first year of life through adolescence. In the year 2018, 192 children under 14 years of age died in Spain from cancer, which means 4 children died per week due to this cause[2]. The most frequent neoplasms from birth to 14 years of age are: leukemias (28%), central nervous system (CNS) tumors (23%) and lymphomas (12%), with a distribution pattern by

Table I. Registered cases according to diagnostic group and age. RNTI-SEHOP data between 1980-2017. Cases not classifiable in ICCC-3 were excluded[1]

0 years		*1-4 years*		*5-9 years*		*10-14 years*		*15-19 years*	
SNS	35.4%	Leukemia*	33.8%	Leukemia*	27.9%	Lymphoma**	21.9%	Bone	24.3%
Leukemia*	13.3%	CNS	19.6%	CNS	27%	Leukemia*	21.1%	Lymphoma**	21.4%
CNS	12.6%	SNS	12.8%	Lymphoma**	17.3%	CNS	20.8%	CNS	15.3%
Retinoblastoma	11.3%	Renal	9.5%	STB	7.2%	Bone	16.7%	Leukemia*	13.9%
Renal	8.5%	Lymphoma**	6.9%	Bone	7.2%	STB	7.6%	STB	10.9%
STB	6.3%	STB	6.2%	Renal	4.4%	Epithelial and melanoma	4.7%	Germ cell***	5.8%
Germ cell***	5.4%	Retinoblastoma	4.7%	SNS	3.7%	Germ cell***	4.5%	Epithelial and melanoma	5.2%

*RNTI: Spanish National Registry of Childhood Tumors. SEHOP: Spanish Society of Pediatric Hematology and Oncology. ICCC: International Classification of Childhood Cancer. CNS: central nervous system. SNS: sympathetic nervous system. STS: soft tissue sarcoma. *Leukemia and myeloproliferative and myelodysplastic diseases. **Lymphoma and reticuloendothelial neoplasms. ***Germ cell, trophoblastic and gonadal.*

sex and age similar to that of the rest of Europe, whilst between 15 and 19 years of age they are: bone tumors (24%), lymphomas (21%) and CNS tumors (15%). The most frequent diagnoses according to the age group are shown in Table I[1].

Patients at risk

Medical history is the most effective tool in identifying cancer predisposition syndromes.

There is a hereditary basis in 8-10% of all neoplasms. Within this percentage, cancer predisposition syndromes (CPS) are included, conforming a heterogeneous group of genetic conditions and immunodeficiencies, which predispose to a greater risk of cancer (Table II). Most of these syndromes are rare and show variable expressiveness within the family members. It is important to identify these patients, as they can benefit from prevention and early detection measures, as well as the possibility of genetic counseling. During history-taking, CPS may be suspected should there be[3]:

- Several cases of cancer within the family, usually of the same type.
- Multi-generational disease cases, presenting at an earlier age than in the general population.
- Presence of tumors in association with developmental defects: generalized or asymmetric body overgrowth, dysmorphic features, congenital malformations or mental retardation.
- Presence of bilateral or multifocal tumors.
- Individuals with more than one primary tumor.
- Presence of rare, benign tumors or cysts associated with CPS.

Warning signs and symptoms

Apparently benign symptomatology, but with atypical presentation or torpid course, may be the beginning of a neoplastic process.

Childhood cancer can manifest in its initial stages, with symptoms similar to frequent and benign processes[4]. The purpose is to recognize when this apparently benign symptomatology may be the beginning of a serious pathology, as well as to identify those findings (red flags) that, in combination with the rest of the data from history and physical examination, should alert us of the possibility of cancer (Table III). For this, it is necessary to listen and pay special attention to parents[5], who in general are the best observers of their children's symptoms, and also to adolescents[6]; taking a complete medical history including personal and family history, and a thorough physical examination.

Qualitative studies highlight the importance of behavioral and affective changes detected by parents, that motivate the first visits to Primary Care prior to the diagnosis of cancer, sometimes in the absence of other signs of alarm[5,7]. Such is the case, that the National Institute for Clinical Excellence (NICE) recommends considering the persistent parental concern regarding their children's symptoms as a reason for study or referral[8]. In Primary Care, the following signs and symptoms have been reported to increase the possibility of cancer: paleness, head and neck masses, abdominal masses, lymphadenopathy, motor abnormalities, bruises and other signs of bleeding, asthenia, headache, visual anomalies, pain and musculoskeletal symptoms. However, except for abdominal masses, the positive predictive value of these symptoms is low, given the low frequency of childhood cancer. Even so, given the severity of the diagnosis, the presence of the aforementioned symptoms, fundamentally when it occurs without a clear cause and leads to an increase in the number of consultations (3 or more in a period of 3 months), should alert of the possibility of a neoplastic process[9]. In this sense, the Pan American Health Organization has published an evaluation strategy, a cancer probability classification and attitude based on the findings of the history and examination shown in Algorithm 1[10].

Headache and other neurological signs and symptoms

Primary CNS tumors are the second most common neoplasia in childhood after leukemias[1], as well as the second leading cause of death from childhood cancer[2]. Their symptoms are due to the invasion and compression of the adjacent nervous tissue, as well as the increase in intracranial pressure due to mass effect or obstructive hydrocephalus (Fig. 1), manifesting a very heterogeneous clinical presentation. Wilne et al.[11] analyzed 74 articles (n = 4,171), identifying up to a total of 56 signs and symptoms at the diagnosis of a CNS

Table II. Cancer predisposition syndromes and associated tumors

Syndrome	*Tumor*	*Syndrome*	*Tumor*
Down's syndrome	AML and ALL	Familial adenomatous polyposis	Medulloblastoma, colorectal cancer, epidermoid cysts, osteomas, FTC, hepatoblastoma, and desmoid tumors
Turner syndrome	Germ cell and leukemia	Peutz-Jegher syndrome	Colon-rectum, stomach and duodenum, pancreas, breast, uterus and gonads
Klinefelter syndrome	Breast adenocarcinoma, gonadal and extragonadal germ cell	Li-Fraumeni syndrome	CNS, ALL, sarcoma, melanoma, neuroblastoma, GI adenocarcinoma, and adrenocortical carcinoma
Trisomy 8	Nephroblastoma, extragonadal germ cell, leukemia, and leiomyosarcoma	Hereditary retinoblastoma	Retinoblastoma, sarcoma, lung, melanoma, leukemia, NHL and CNS
Xeroderma pigmentosum	CNS, carcinoma, adenocarcinoma, germ cell, leukemia, melanoma and other skin tumors and RMS	Familial neuroblastoma	Neuroblastoma
Bloom syndrome	GI and skin carcinomas, breast adenocarcinoma, ALL, NHL and cervix	Ondine syndrome	Neuroblastoma
Fanconi anemia	AML, CNS, squamous cell carcinoma, esophagus, and hepatocellular	MEN 1	Parathyroid, pituitary, adrenal adenoma, gastrinoma, carcinoid tumor, lipoma, and facial fibroangiofibroma
Ataxia Telangiectasia	CNS, ovarian and breast adenocarcinoma, lymphoma, CLL, ALL, gastric carcinoma, hepatocellular, melanoma and leiomyosarcoma	MEN 2A	Pheochromocytoma, MTC, and parathyroid tumor
Tuberous sclerosis	Renal, CNS, facial angiofibroma, thyroid adenoma and RMS	MEN 2B	MTC, pheochromocytoma, and cutaneomucosal neuromas
Neurofibromatosis type 1	CNS, optic glioma, medullary neurofibroma, neurofibroma, neurofibrosarcoma, pheochromocytoma, paraganglioma, and carcinoid	Familial malignant melanoma	Melanoma and pancreas
Type 2 neurofibromatosis	CNS, neurofibroma and vestibular schwannoma	Denys-Drash syndrome	Wilms tumor and gonadoblastoma
Von Hippel-Lindau syndrome	Renal carcinoma, pheochromocytoma, CNS paraganglioma and hemangioblastoma	Beckwith Wiedemann syndrome	Wilms tumor, gonadoblastoma, neuroblastoma, hepatoblastoma, hepatocellular carcinoma, adrenocortical carcinoma and RMS
Turcot syndrome	Colon adenocarcinoma, glioblastoma, medulloblastoma, neuroblastoma, and leukemia	WAGR syndrome	Wilms tumor and gonadoblastoma
Carney complex	Uterus, thyroid leiomyoma, cardiac myxoma, adrenocortical, testicular and pituitary carcinoma	Autoimmune lymphoproliferative syndrome	Lymphoma and hepatocellular carcinoma
Cowden syndrome	Thyroid, breast, ovary, kidney, endometrium, melanoma and CNS	X-linked lymphoproliferative syndrome	NHL
Diamond-Blackfand syndrome	Leukemia	Sotos syndrome	Wilms tumor
Severe congenital neutropenia	AML	Congenital dyskeratosis	Leukemia, squamous cell carcinoma and pancreas

AML: acute myeloid leukemia. ALL: acute lymphoblastic leukemia. CNS: central nervous system. RMS: rhabdomyosarcoma. GI: gastrointestinal. NHL: non-Hodgkin lymphoma. CLL: chronic lymphatic leukemia. CPT: papillary thyroid carcinoma. FTC: follicular thyroid carcinoma. MTC: medullary thyroid carcinoma.

Table III. Warning Signs of Childhood Cancer[4]

Signs and symptoms	*Suspicious clinical features*
Paleness, fatigue and malaise	Especially if it is persistent and if it is associated with signs of bone marrow infiltration (unexplained fever, recurrent infections, bleeding diathesis) and / or lymphadenopathy
Fever	Prolonged (> 2 weeks) without apparent justification, associated with weight loss, night sweats, paleness, petechiae, mass, bone pain and lymphadenopathies
Recurrent or persistent infections	Associated with: paleness, petechiae, weight loss, bone pain, lymphadenopathies, hepatosplenomegaly or palpable mass
Anorexia and weight loss	Prolonged and unjustified, especially if accompanied by weight loss and other warning signs (recurrent infections, fever, paleness, lymphadenopathies, hepatosplenomegaly)
Localized lymphadenopathies Generalized or localized	Persistent or progressive that do not resolve in 4-6 weeks or unresponsive to antibiotic treatment; size> 2 cm, hard, painless, supraclavicular or epitrochlear Associated with: fever, night sweats, weight loss, malaise, paleness and hepatosplenomegaly
Hemorrhagic manifestations (petechiae, ecchymosis, recurrent epistaxis, bleeding gums)	Persistent or combined with other signs of bone marrow infiltration (paleness, fatigue, recurrent infections)
Headache	Of recent onset, in the morning or that awakens during the night, without a history of migraine, associated with vomiting or neurological symptoms (cranial palsy, motor or sensory signs), occipital location and worsening when lying down
Impaired school performance and mood changes	Of recent onset, progressive and not justified
Palpable abdominal mass	Any mass (except in the neonatal period) is suspicious for malignancy, especially when associated with vomiting, abdominal pain, constipation, hematuria or hypertension
Hepatomegaly	Must always be investigated, even in asymptomatic cases
Vomiting	Persistent or recurring; associated with morning headache or abdominal mass
Bone pain, arthralgia / arthritis, limp or refusal to walk	Bone pain that awakens at night, duration > 2 weeks, localized, associated with inflammation, no improvement with NSAIDs
Back pain, kyphoscoliosis, lordosis and torticollis	Back pain of sudden onset, age < 4 years, worsening at night, associated with fever or neurological symptoms, without traumatic history and not improving with NSAIDs
Mass or lump in extremities, head, neck, or trunk	Any palpable mass of recent appearance, located deep in the fascia, not painful, hard, > 2 cm in diameter and associated with regional lymphadenopathies
Urinary retention / enuresis	Recent, associated with neurological symptoms or abdominal mass
Scrotal mass or swelling	Recent; isolated right varicocele
Swollen / bleeding gums	Not justified
Dermatological manifestations	Eczema that does not respond to treatment; subcutaneous nodules

NSAIDs: non-steroidal anti-inflammatory drugs.

tumor, which depended on age, location and history of neurofibromatosis (NF). For intracranial tumors, excluding NF, the most frequent symptoms were: headache, nausea and vomiting, abnormality of gait and coordination, and papilledema. In intracranial tumors associated with NF these were: decreased visual acuity, exophthalmos, optic atrophy and strabismus. In intracranial tumors in children under 4 years they were: macrocephaly, nausea and vomiting, irritability, lethargy and ataxia. And in spinal cord tumors they were: back pain, gait and coordination abnormality, spinal deformity, focal weakness and sphincter alterations. Given this clinical variability, they subsequently studied the evolution of symptoms in a retrospective cohort (n = 139), describing a progressive increase in the number of symptoms. Thus, half of the patients went from one symptom at the beginning of the process to six at the diagnosis of the tumor[12]. In Primary Care, we must be alert to patients with non-resolving symptoms or in which new ones are associated, especially: visual, motor, endocrine or behavioral, as well as signs of intracranial hypertension[12-14]. In this line, Ansell et al.[15] described the reasons for consultation in Primary Care, from birth to the

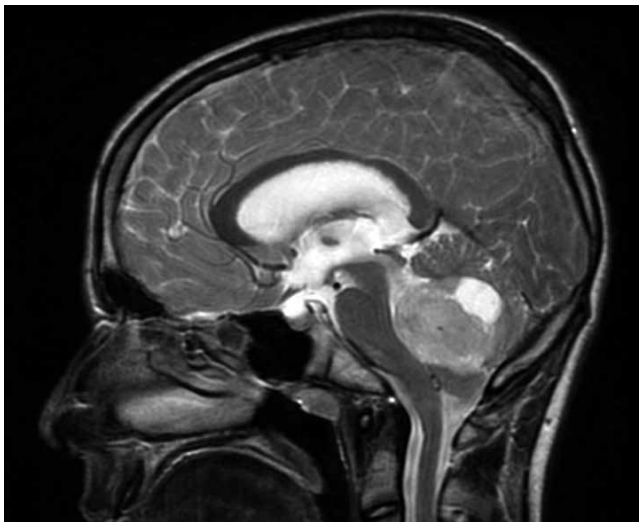

Figure 1. Sagittal MRI showing a mass in the posterior fossa compatible with medulloblastoma. The 13-year-old patient presented with headache and papilledema.

diagnosis of a CNS tumor in a series of patients, comparing it with a control group. They observed how the cases consulted three times more often for a sign or symptom suggestive of a CNS tumor, reaching seven times more when they associated two or more symptoms.

The Children's Brain Tumour Research Centre group has developed an evidence-based clinical guide[16] (Table IV), as well as the awareness strategy "HeadSmart: be brain tumours aware" (https://www.headsmart.org.uk/), which has shown positive results in reducing the time from the onset of symptoms to diagnosis (median 14 to 6.7 weeks), as well as the time from the first consultation to an imaging test (3.3 to 1.4 weeks)[17].

Fever and constitutional symptoms

Fever is one of the most frequent reasons for consultation in Pediatrics, being, in most cases, of infectious etiology. Only 6% of the cases of fever of unknown origin correspond to neoplasms[18]. This fever can be of tumor origin (Ewing's sarcoma, neuroblastoma, Hodking's lymphoma...) or due to infections secondary to the alteration of the immune system due to cancer, as can occur in leukemias.

Leukemia is the most common pediatric tumor[1]. Clarke et al.[19] analyzed the symptoms at the diagnosis of leukemia in childhood and adolescence in 33 studies (n = 3,084), and identified a total of 95 signs and symptoms, of which five were present in more than half of the patients: hepatomegaly, splenomegaly, paleness, fever and bruising. In addition, between a third and a half of the patients presented: recurrent infections, asthenia, pain in the extremities, hepatosplenomegaly, hematomas / petechiae, lymphadenopathies, bleeding tendency and skin rash. These findings highlight the importance of performing a complete physical examination in children with common symptoms, such as fever, but with a torpid or persistent course, paying special attention to abdominal palpation, lymphadenopathy search and careful skin examination. Despite the fact that leukemia is the most frequent pediatric cancer, there is currently no evidence of the predictive value of clinical data at the individual level, or of their combination. NICE guidelines recommend that pediatric patients with fever of unclear cause or in combination with unjustified clinical data such as: paleness, asthenia, lymphadenopathies, splenomegaly, osteoarticular pain, bruising, night sweats or weight loss, should be evaluated with a full blood count and peripheral blood smear within 48 hours; in the case of associating petechiae or unexplained hepatosplenomegaly, immediate referral is recommended[8].

Lymphadenopathies

Lymph nodes are dynamic structures that change in size during children´s growth, usually in response to infections. During childhood, palpation of small lymph nodes in cervical, axillary, or inguinal regions is normal. An increase in size above 1 cm in cervical and axillary nodes, 1.5 cm in inguinal and 0.5 cm in epitrochlear nodes, as well as stone-like consistency, irregular surface, existence of skin ulceration or fixation is considered pathological[20] (Fig. 2). Lymphadenopathies are generalized, when they extend beyond more than 2 non-contiguous ganglion chains, and localized, when they appear in a single region. According to the course in terms of length of time, we distinguish between acute (less than three weeks) and subacute / chronic (more than three weeks / months)[21]. In the history, we should inquire for: the age of the patient, the form of onset, the time of progression and the speed of growth, as well as the presence of recent or recurrent infections, contact with sick people, associated symptoms, previous antibiotic treatments, similar episodes, vaccination status, medications, contact with animals or recent travels. A complete physical examination should be performed, looking for signs of systemic disease and paying special attention to the presence of skin lesions, paleness, signs of bleeding, oropharyngeal or

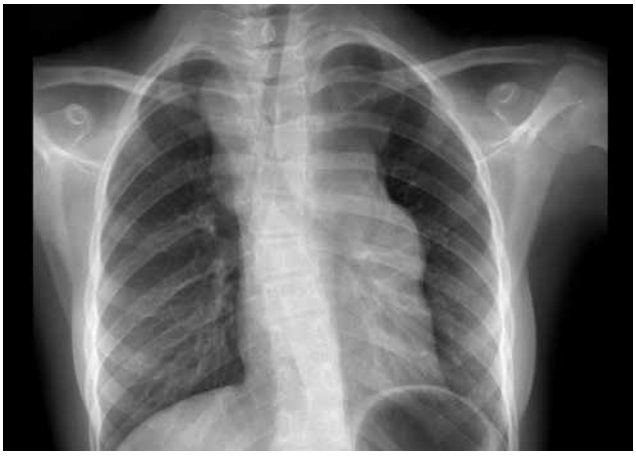

Figure 2. Mediastinal widening in a 12-year-old patient diagnosed with Hodgkin's lymphoma. Clinically, she had multiple adherent, non-tender and larger than 2 cm laterocervical and supraclavicular lymphadenopathies.

Table IV. Guide to the Diagnosis of Central Nervous System (CNS) Tumors in Children[16]

Consider CNS tumor in every child that presents:

- **Headache**
- **Nausea and vomiting**
- **Visual signs and symptoms**
  - Reduced visual field and / or acuity
  - Abnormal eye movements
  - Abnormal fundus
- **Motor signs and symptoms**
  - Gait disorder
  - Coordination disorder
  - Focal motor weakness
- **Impaired growth and development**
  - Growth failure (weight / height)
  - Early / delayed puberty
- **Behavioral changes**
- **Diabetes insipidus**
- **Seizures**
- **Abnormal consciousness**

Special consideration must be given to the association of various symptoms and the existence of predisposing factors

Imperative physical examination

- **Weight and height**
- **Head circumference** (<2 years)
- **Pubertal development**
- **Psychomotor development** (<5 years)
- **Visual**: pupillary response, visual acuity, ocular motility, fundus and visual field
- **Motor**: sitting and crawling in infants; gait and run; coordination, fine motor skills (picking up small objects, writing)

A normal physical examination does not exclude a brain tumor

Headache	***Nausea Vomiting***	***Visual***	***Motor***	***Growth/ Development/ Behaviour***
- Recent - Persistent > 4 weeks - No predominance at a particular time of the day - Observe behavior (< 4 years) - Changes in the characteristics of previous headache	- Persistent > 2 weeks	- Persistent > 2 weeks - Visual evaluation. If not collaborating and < 4 years of age, direct referral to ophthalmologist (within 2 weeks)	- Persistent > 2 weeks - Loss of motor skills - Motor evaluation	Two of the following: - Failure to thrive - Delayed / early puberty - Polyuria and polydipsia / secondary enuresis (diabetes insipidus manifestations) - Drowsiness in unusual situations
Imaging test indication (maximum interval of 4 weeks)				
- Persistent and nocturnal awakening - Morning predominance - Under 4 years old - Associated with confusion or disorientation	- Vomiting when getting up (in the morning and after naps)	- Papilledema - Optic atrophy - Recent nystagmus - Visual field reduction - Decreased visual acuity not attributable to a refractive error - Proptosis - Recent strabismus	- Loss of motor skills - Feebleness - Ataxia - Bell's palsy that does not improve in 4 weeks - Dysphagia (except local cause)	
Longer time to diagnosis associated with:				
- No reevaluation of patient with a previous headache with changing characteristics	- Attribution of vomiting to infection, in the absence of other suggestive data: diarrhea, epidemic environment...	- Failure in the evaluation of a non-cooperative patient / < 4 years of age - Communication failure between optometrist-pediatrician-ophthalmologist	- Attribution of abnormal balance or gait to ear process without conclusive examination - Failure to identify dysphagia secondary to CNS tumor as a cause of recurrent respiratory infections.	- Attribution of failure to thrive and vomiting to gastrointestinal causes without other confirmatory findings - Not having excluded diabetes insipidus in children with polyuria and polydipsia

conjunctival lesions, hepatosplenomegaly, and abdominal masses. Adenopathies will be evaluated based on their size, location, tenderness, consistency, mobility, local inflammatory signs, and presence of skin fistulas. We must systematically palpate all accessible ganglion chains: occipital, retroauricular, preauricular, parotid, tonsillar, submandibular, submental, anterior and posterior neck, supraclavicular, infraclavicular, axillary, epitrochlear, inguinal and popliteal. Warning signs in the evaluation of adenopathies are: size greater than 3 cm, rapid growth in the absence of inflammatory signs, hard consistency, fixation to deep planes, supraclavicular, axillary, genera-

Table V. Mediastinal compartments, anatomical structures and types of mediastinal masses according to their location

Location	*Anatomy*	*Non-neoplastic*	*Neoplastic origin*
Anterior mediastinum	- Thymus - Vagus nerve - Recurrent laryngeal nerve - Thoracic duct - Superior vena cava - Lymph nodes	- Aortic aneurysm - Thymic hyperplasia - Lipoma - Angiomas	- **NH T type lymphomas** - Leukemia T - Thymoma - Germ cell tumors (teratoma, teratocarcinoma, seminoma, choriocarcinoma, embryonal carcinoma) - Thyroid tumors - Parathyroid tumors
Middle mediastinum	- Heart - Pericardium - Brachiocephalic trunk - Tracheal bifurcation - Tracheobronchial lymph nodes - Main bronchi - Transverse and ascending aorta	- Lymphadenopathies secondary to infections - Bronchogenic cysts - Pericardial cysts - Enteric cysts	- T leukemia or lymphoma - **Hodgkin lymphoma** - Metastatic tumors (neuroblastoma, rhabdomyosarcoma, germ cell tumors) - Abdominal extension neoplasms (neuroblastoma)
Posterior mediastinum	- Thoracic aorta - Thoracic duct - Azygos vein - Esophagus - Lymph nodes - Sympathetic autonomic ganglia - Anterior aspect of vertebral bodies	- Enteric cysts - Bronchogenic cysts - Esophageal duplication - Neurofibroma - Myelomeningocele, anterior diaphragmatic hernia - Paravertebral abscess	- Neurogenic tumors (**neuroblastoma**, ganglioneuroma, neurofibroma) - Ewing type sarcomas

lized or confluent location, as well as constitutional symptoms, the presence of abdominal masses, hard hepatosplenomegaly, signs of respiratory distress, paleness, jaundice or bleeding[8,20-22].

Mediastinal mass

Mediastinal masses in childhood are rare and, in most cases, are malignant. The most frequent location is the anterior mediastinum and the most frequent etiology is lymphoma[23,24]. A thorough clinical evaluation and a high index of suspicion are important for an early diagnosis. Upon clinical suspicion, immediate referral to a hospital center to complete the study is recommended[8,23].

From an anatomical point of view, the mediastinum is divided into three compartments: anterior, middle, and posterior. The location of the mass will guide the diagnosis (Table V). The most frequent neoplasms according to their location are: acute lymphoblastic leukemia and T lymphoma (Fig. 3) in the anterior mediastinum; Hodgkin lymphoma in the middle mediastinum; and neurogenic tumors (neuroblastoma and ganglioneuroma) in the posterior mediastinum. Posterior mediastinal masses (neuroblastoma) are more common in infants and young children, while anterior mediastinal masses (leukemias, lymphomas) are more common in older children and adolescents[24].

A high percentage of patients are asymptomatic at diagnosis. In symptomatic cases, the symptoms are secondary to compression of adjacent structures, so the symptoms depend on the location of the mass, its size, and the rate of growth. Compression of the airway is the most frequent symptom, giving rise to nonspecific symptoms, such as: stridor, non-productive cough, wheezing, recurrent respiratory infections, chest pain and respiratory distress that often simulate frequent respiratory diseases, such as asthma or laryngitis. Esophageal compression leads to dysphagia. Compression of the spinal cord (common in neuroblastoma) results in band or radicular back pain that increases with Valsalva, gait weakness, loss of strength and sensory and sphincter alterations. Compression of the superior vena cava (characteristic of leukemias and T lymphomas) manifests with: facial plethora, headache, blurred vision, cough, chest pain, orthopnea that increases with Valsalva, hypotension and heart failure. Compression of the phrenic leads to hemidiaphragmatic elevation. Finally, injury to the sympathetic pathway (especially neuroblastomas) can cause Horner syndrome (ptosis, miosis, and eno-

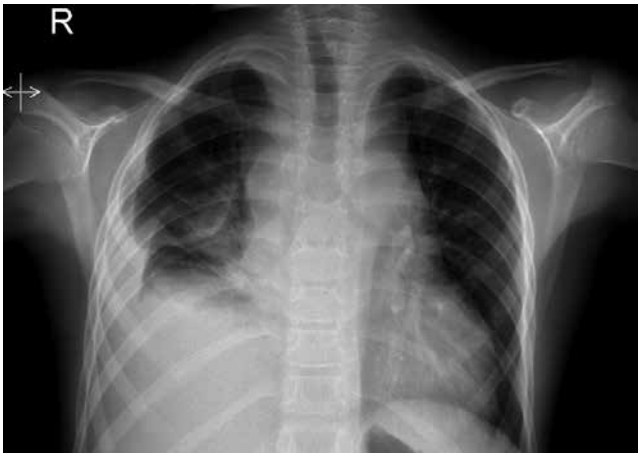

Figure 3. Anterior mediastinal mass in a 12-year-old boy with T-leukemia. He reported a 3 day course of asthenia and bilateral eyelid edema, as well as 48 hours of bruising, ecchymosis and petechiae in face, neck and upper arm.

Table VI. Benign and malignant abdominal masses depending on age

Neonates and infants under 1 year

Non-neoplastic	*Neoplastic origin*
Genitourinary:	*Genitourinary:*
- Hydronephrosis	- Wilms tumor
- Multicystic dysplastic kidney	- Mesoblastic nephroma
- Polycystic kidney disease	- Nephroblastomatosis
- Horseshoe kidney	*Adrenal:*
- Urachal cyst	- Neuroblastoma
Adrenal:	*Liver / spleen:*
- Adrenal hemorrhage	- Liver tumors (hemangioma, hemangioendothelioma, mesenchymal hamartoma due to hepatoblastoma), tumor metastases (neuroblastoma or Wilms tumor)
Liver / spleen:	*Genital:*
- Congestive heart failure	- Sacrococcygeal teratoma
- Congenital infections	
- Deposit diseases	
- Choledochal cyst	
- Liver cyst	
Genital:	
- Ovarian cyst	
- Hydrometrocolpos	
Gastrointestinal:	
- Feces, meconium plug	
- Intestinal duplication	
- Mesenteric cyst	
- Intussusception	
- Intestinal stenosis / atresia	
- Malrotation / volvulus	

Between 1-10 years

Genitourinary:	*Genitourinary:*
- Hydronephrosis	- Kidney tumor (nephroblastoma, rhabdoid tumor, clear cell sarcoma of the kidney)
- Bladder distention	- Rhabdomyosarcoma
- Ovarian cyst	*Adrenal:*
Liver / spleen:	- Neuroblastoma
- Congestive heart failure	*Liver / spleen:*
- Metabolic disturbances	- Liver tumor (hemangioma, hemangioendothelioma, mesenchymal hamartoma, hepatoblastoma, tumor metastases due to neuroblastoma or nephroblastoma)
- Infections	*Others:*
Gastrointestinal:	- Teratoma
- Feces	- Lymphoma
- Intestinal duplication	- Rhabdomyosarcoma
- Mesenteric cyst	
- Intussusception	
- Volvulus /Malrotation	

Older than 10 years

Genitourinary:	*Genitourinary:*
- Hydronephrosis	- Rhabdomyosarcoma
- Bladder distention	- Ovarian cyst (teratoma / dermoid cyst)
- Pregnancy / ectopic pregnancy	- Germ cell tumor
- Pelvic inflammatory disease	- Renal carcinoma
Liver / spleen:	*Liver / spleen:*
- Congestive heart failure	- Hepatocellular carcinoma
- Metabolic disturbances	- Tumor metastases
- Infections	*Gastrointestinal:*
Gastrointestinal:	- Colorectal carcinoma
- Feces	*Others:*
- Inflammatory pathology (appendicitis...)	- Lymphoma
	- Rhabdomyosarcoma
	- Soft tissue sarcoma, PNET / Ewing sarcoma
	- Desmoplastic small round cell tumor

phthalmos). And, in turn, we can find systemic symptoms secondary to the tumor process itself. Compression of the phrenic leads to hemidiaphragmatic elevation. Finally, injury of the sympathetic pathway (especially neuroblastomas) can cause Horner syndrome (ptosis, miosis, and enophthalmos). In addition, we can find systemic symptoms secondary to the tumor process itself.

We must bear in mind that treatment prior to diagnosis with systemic corticosteroids in patients with hematological malignancies may have diagnostic and prognostic implications, and precipitate serious complications, such as tumor lysis syndrome. For this reason, in patients with atypical respiratory symptoms or laryngitis in older children, performing a chest X-ray prior to starting corticosteroid treatment is recommended[23,25].

Abdominal mass

The finding of an abdominal mass is one of the most frequent forms of presentation of neoplasms in childhood. Although they may be of benign etiology, all patients with an abdominal mass must be evaluated with the suspicion of malignancy and referred to a specialized center within 48 hours[8].

An abdominal mass is often asymptomatic, and is usually detected accidentally by the parents or in a routine examination. In the history, we will take into account the patient's age (Table VI), the associated symptoms, their intensity and duration, taking into account which rapidly evolving symptoms are suggestive of malignancy[26,27]. The most frequent presentation symptoms are: pain, organ dysfunction due to mass effect (intestinal or urinary obstruction), hematuria (nephroblastoma) and systemic symptoms (night sweats, fever, asthenia, weight loss or bone pain...). The most frequent etiology involves: genitourinary congenital malformations in children under one year of age; neuroblastoma (Fig. 4) and nephroblastoma (Fig. 5) between one and five years; and non-Hodgkin lymphoma (NHL) in older children and adolescents. In this age group, Burkitt-type NHL presents as: a rapidly growing abdominal mass that associates abdominal distention and pain, obstructive symptoms, intussusception, and meta-

bolic alterations secondary to tumor lysis[26]. In girls and adolescents, we will take into account ovarian tumors and pregnancy. In the personal history, factors such as prematurity and low birth weight (hepatoblastoma), should also be assessed.

Physical examination should be performed with the patient relaxed and calm. It must be meticulous, checking vital signs, including blood pressure[27]. On inspection, we will look for irregularities on the abdominal surface. On palpation, we must take into account that, in healthy patients, especially infants, some structures may be palpable, such as: liver, spleen, kidneys, abdominal aorta, sigmoid colon, feces and / or spine[28]. It is important to establish the location, size, shape, and contour of the mass, its adherence to deep planes, as well as the presence of tenderness. Depending on the location it should be considered that: palpable masses in the right upper quadrant are usually of hepatic, renal or adrenal origin; those in the upper left quadrant often depend on the spleen and may be secondary to metastatic infiltration; and those located in the hypogastrium, are usually secondary to ovarian tumors or intestinal lymphomas. In the patient with suspected neuroblastoma, a complete neurological examination is necessary due to the possibility of invasion of the medullary canal. Other examination signs that can guide the diagnosis are: aniridia, hemihypertrophy and genitourinary malformations (nephroblastoma); subcutaneous nodules, periorbital ecchymoses, proptosis, intractable watery diarrhea, Horner syndrome or opsoclonus-myoclonus syndrome (neuroblastoma); precocious puberty, feminization or virilization (hepatic, gonadal, adrenal masses or germ tumors); and Cushing phenotype (neoplasms of the adrenal cortex).

Soft tissue and skin masses

Soft tissue sarcomas (STS) are a heterogeneous group of tumors that originate from primitive mesenchymal cells. They are subdivided into rhabdomyosarcoma (RBM) and non-rhabdomyosarcoma sarcomas. RBM is the most frequent, it has its origin in the primitive mesenchymal cells involved in the development of skeletal muscle,

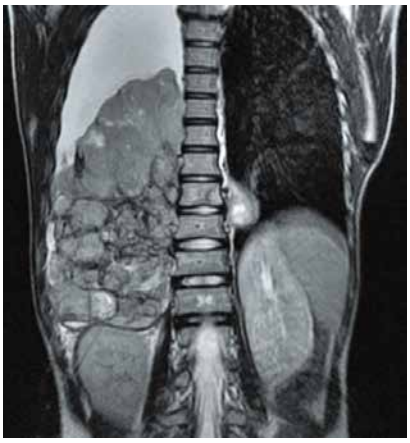

Figure 4. Neuroblastoma in a 7-year-old patient who reported weeks of rib pain associated with asthenia and anorexia in the most recent days.

and it presents its maximum incidence around the age of five years and in adolescence. It is subdivided into: embryonal, alveolar and pleomorphic. On the other hand, non-rhabdomyosarcoma sarcomas are more common in older children and adolescents.

STS can appear in any anatomical location, the most frequent being: the genitourinary region, head and neck, and extremities. The clinical presentation depends on the location, size and adjacent structures. An unexplained tumor in any location with any of the following characteristics is suspicious of STS: diameter greater than 2 cm, fixation to deep planes, increased consistency, progressive growth, and presence of regional lymphadenopathies[4]. In the head, orbital locations usually develop proptosis and a differential diagnosis must be made with benign pathologies, such as orbital cellulitis. Parameningeal locations can lead to nasal, sinus, or ear

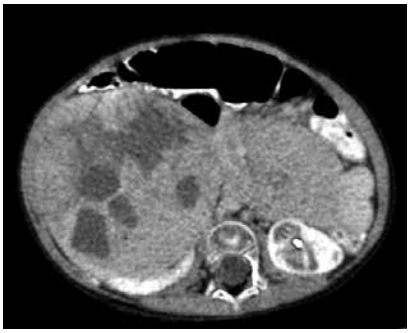

Figure 5. Right Wilms tumor. The 2-year-old patient consulted because the parents palpated the abdominal mass while dressing her.

obstruction, persistent mucopurulent discharge, or cranial nerve involvement. In the genitourinary region, it can present as: hematuria, voiding syndrome, constipation, pelvic mass or increased testicular size. The botryoid variety is a subtype of embryonic RMS characterized by multiple polypoid projections that form clusters of gelatinous and friable consistency, that develop under the mucosal surface of body orifices, such as vagina and nose.

When a soft tissue tumor is suspected, NICE guidelines recommend performing an ultrasound within 48 hours[8].

Musculoskeletal symptoms and signs

Musculoskeletal pain is a frequent reason for consultation in Primary Care. Its etiology varies with age, the most frequent causes being traumatic. The differential diagnosis will include overuse syndromes and osteochondroses. Less frequently, but highly important as their diagnosis delay can increase morbidity, are neoplasms and osteoarticular infections. Among the most frequent neoplasms that present with bone and / or joint pain, primary bone tumors, neuroblastomas, NHL and leukemias, can be found.

Patients with primary bone tumors, such as osteosarcoma or Ewing's sarcoma, frequently present with localized, persistent, asymmetric, progressive bone pain that responds poorly to common analgesics and may wake the child up at night. They can associate a palpable indurated mass fixed to deep planes and of rapid and progressive growth and, occasionally, a pathological fracture can occur. Generalized musculoskeletal pain manifests as: lower limb pain, back pain, arthralgia or arthritis. The tumors that produce it are leukemias, especially lymphoblastic leukemia and bone or medullary metastases of tumors, such as Ewing's sarcoma or neuroblastoma.

Several authors[29-31] have highlighted the relevance of incorporating leukemias and bone tumors in the differential diagnosis of patients with suspected osteomyelitis or rheumatological diseases. Leukemias that present with joint symptoms (generally in the form of asymmetric oligoarthritis) are less frequently associated with typical

leukemia symptoms, such as: constitutional syndrome, hepatosplenomegaly or cytopenia, which makes diagnosis difficult[29]. In the evaluation of patients with musculoskeletal symptoms, the association of leukopenia (less than 4 x 10^9 / L), platelets in the lower limit of normality (150-250 x 10^9 / L) and a history of nocturnal pain, represents a sensitivity of 100% and specificity of 85% in the diagnosis of leukemia[30]. The importance of an accurate diagnosis prior to the start of steroid treatment should be noted, given the possibility of masking a hematological neoplasm or triggering a tumor lysis syndrome. For this reason, some authors suggest performing a bone marrow study prior to initiating treatment with steroids, in those patients with suspected rheumatological disease and atypical data[31].

A complete medical history that includes: characterization of the pain (onset, location, duration, intensity, number of affected joints); presence of other accompanying symptoms (inflammation, increased temperature, joint instability); precipitating factors (previous infection or trauma); and associated systemic symptoms, as well as a thorough physical examination, will guide the diagnosis. In a patient with bone and / or joint pain with suspected cancer, an X-ray as well as a full blood count and peripheral blood smear shall be performed within 48 hours. In case of a pathological X-ray, the patient should be referred to a specialized center within 48 hours. When leukemia is suspected (cytopenia of two or more cell lines and / or blasts), referral will be immediate[8].

Eye disorders

Retinoblastoma is the most common ocular neoplasm, representing 3% of childhood tumors[1]. It is usually diagnosed between the first and third year of life, and 95% of them before the age of 5 years[1]. 30% are bilateral and 40% hereditary. Leukocoria is the presenting sign in more than half of the cases, and it appears as a consequence of the presence of a mass located behind the crystalline lens. In the differential diagnosis of leukocoria, in addition to retinoblastoma, congenital cataracts (history of infection in pregnancy, such as toxoplasmosis, should be investigated) and Coats disease (retinal telangiectasia with deposition of intraretinal or subretinal exudates that affects younger children). Other symptoms and signs that should alert us include: strabismus, loss of visual acuity, eye pain or proptosis. In addition to retinoblastoma, other tumors that can manifest as proptosis include: neuroblastoma, rhabdomyosarcoma, lymphoma, and histiocytosis. The successful management of retinoblastoma depends on the ability to detect the disease while it still remains intraocular[32]. Hence, it is very important to test for the red reflex in all newborns and in each programmed child health visit. An abnormal result of the red reflex examination is an indication for preferential referral (in less than two weeks) to the ophthalmologist[8]. Patients with a family history of retinoblastoma must be referred from birth for close ophthalmological follow-up[3].

Another ocular manifestation of cancer is the paraneoplastic opsoclonus-myoclonus syndrome, which is associated with neuroblastoma in 50% of cases. It is characterized by multidirectional, involuntary and chaotic rapid eye movements, persistent during sleep, myoclonus, ataxia, and behavioral disturbances.

Time lapse to childhood cancer diagnosis

Decreasing the time to diagnosis has prognostic implications in some childhood tumors.

The most effective strategy to reduce the morbidity and mortality of childhood cancer is to focus, both on the reduction of the time to diagnosis (TD), understood as the time elapsed from the onset of symptoms to the diagnosis of cancer[33] (Fig. 6), as in the early initiation of treatment based on scientific evidence. Therefore, the recognition of alarm symptoms by families and Primary Care professionals, as well as easy access to the latter, is a priority. Screenings in childhood are usually not helpful, unless the child has a high risk of cancer associated with hereditary disorders. Among factors that have been related to TD, the following stand out: the patient's age (the older, the greater the TD); the type of tumor (CNS, bone, germ cells and retinoblastomas have longer TD compared to leukemia and kidney tumors); and tumor biology[33-35]. The relationship of TD with survival is complex. Thus, some authors[35,36] indicate that it is precisely the biology of the tumor, the factor that most influences TD and survival. In any case, there is extensive literature supporting a positive correlation between improved survival and early diagnosis in tumors such as retinoblastoma[35], being this correlation more ambiguous for CNS and other solid tumors, probably in relation to high-grade tumors having a more abrupt onset of prediagnostic symptoms and, therefore, a shorter TD[37]. In the group of adolescents and young adults, although females more frequently consult physicians, they have more prolonged TD. Bone tumors and lymphomas have longer TD, probably due to the non-specific clinical presentation of these types of cancer[6].

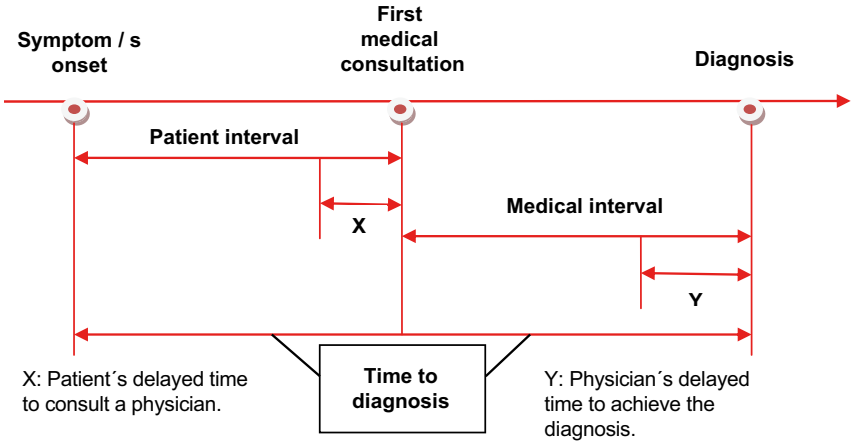

Figure 6. Time to diagnosis in childhood cancer. Modified from Lethaby et al[33].

It should be noted how, in the COVID-19 pandemic situation, several publications have warned of the increase in TD of childhood cancer in neighboring countries[38,39].

Role of the Primary Care pediatrician

The Primary Care pediatrician shares the responsibility of reducing TD, identifying those patients suspected of cancer and making an early referral to specialized care. This decrease in TD may have a prognostic role for some tumors and, in addition, contributes to the reduction of anxiety and stress experienced by patients and their families during the difficult period prior to the diagnosis of childhood cancer[5].

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A must-read. Clinical guide for the suspicion and early diagnosis of tumors of the central nervous system.

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Very interesting. Strategy launched in 2011 in the United Kingdom, aimed at healthcare professionals and the general public, with the aim of reducing the time interval from the onset of symptoms to the diagnosis of a CNS tumor in pediatric patients.

Clinical case

7-year-old patient who presents with a 3-day course of frontal, evening headache, as well as progressive 2-week loss of vision in the left eye.

Personal history

Normal course pregnancy. Vaginal delivery. Normal neonatal period. Normal psychomotor development. Up-to-date vaccination schedule.

Family background

Mother: 32 years old, healthy, gestations: 1/miscarriages: 0/life births: 1. Father: 38 years old, healthy.

Physical examination

HR: 90 bpm. RR: 18 rpm. BP: 100/60 mmHg. Sat: 97%. Height: 122 cm (50th centile). Weight: 24 kg (50th centile). Good general condition. Well hydrated and perfused. No rashes or petechiae. No significant lymphadenopathies. Cardiopulmonary auscultation: normal. Abdomen: soft, non-tender, no masses or megalies. Neurological: Glasgow 15, with normal cranial nerves, tone, strength, sensitivity, tendon reflexes and gait. No dysmetria or dysdiadochokinesia. Ophthalmological examination: left eye with decreased visual acuity, signs of papillary atrophy, as well as left temporal hemianopsia.

Complementary tests

Normal full blood count, biochemistry and coagulation. A brain MRI was performed which evidenced a midline, suprasellar, multicystic, heterogeneous mass measuring 40 x 36 x 39 mm (Fig. 7), with intense and heterogeneous enhancement following contrast administration (Fig. 8). Normal ventricular system, without signs of hydrocephalus.

Diagnosis

Craniopharyngioma (adamantinomatous pattern).

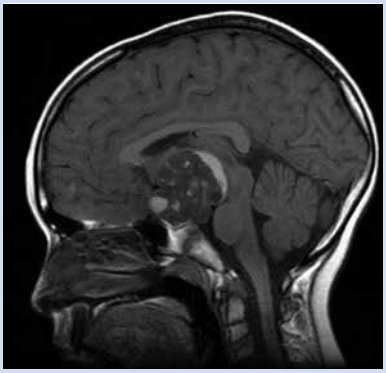


Figure 7. Heterogeneous midline, suprasellar, multicystic mass measuring 40 x 36 x 39 mm.

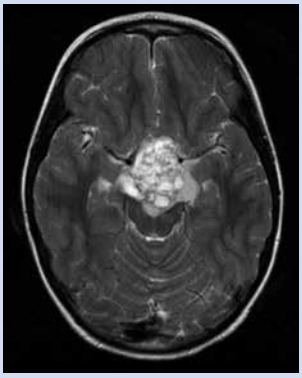
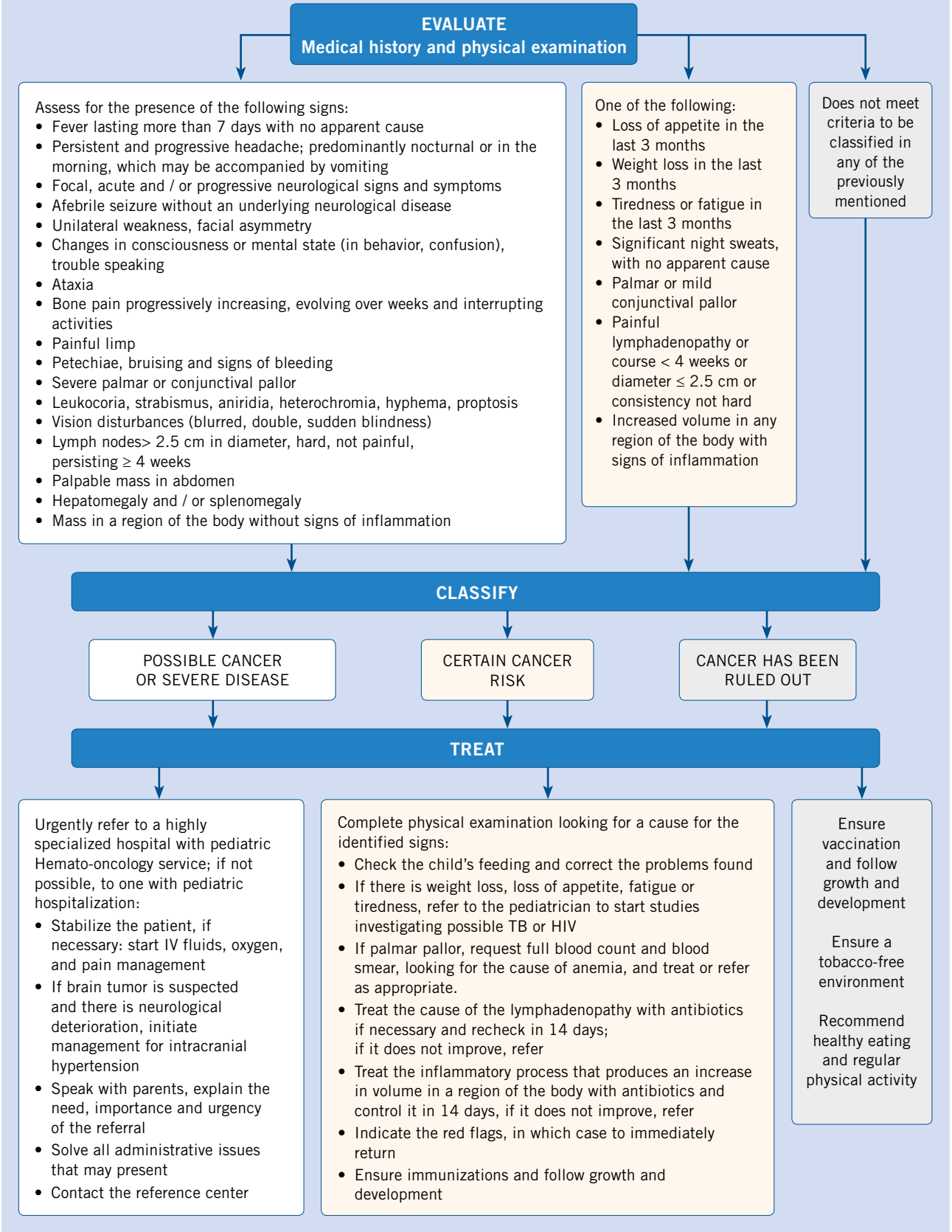


Figure 8. Midline mass with intense and heterogeneous enhancement following contrast administration.

Algorithm. Pan American Health Organization childhood cancer probability classification[10]



Accreditation quiz

Subsequently, the following accreditation quiz of Pediatría Integral collects questions on this topic, which must be answered online through the website: www.sepeap.org.
In order to obtain certification by the Spanish "formación continuada" national health system for health professionals, 85% of the questions must be answered correctly. The accreditation quizzes of the different numbers of the journal may be submitted during the period indicated in the "on-line" quiz.

How to suspect cancer in Primary Care

9. Indicate the CORRECT answer regarding childhood cancer:

a. Given the increase in its incidence in recent decades, it has become a common diagnosis in the Primary Care consultation.

b. In most cases, it presents with specific warning signs and symptoms.

c. Given advances in diagnosis and treatment, it is a rare cause of death in children.

d. Certain chromosomal diseases are associated with an increased risk of developing tumors.

e. Neuroblastoma is the most common solid tumor in childhood.

10. A 6-year-old boy attends our office for a two-month course of arthralgias, without associating fever or weight loss. The mother has noticed that he is slightly more tired and with a poor appetite, but since COVID-19 lockdown he has barely done physical activity, she has not given it much importance. She states that, lately, he has more "bruises" than usual. On examination he presents slight skin pallor, but rosy mucous membranes, some punctate petechiae on the palate and bruises in different stages on the lower limbs; with no other abnormalities. In view of this case our ATTITUDE should be:

a. To prescribe anti-inflammatory medication and rest for 1 week and check him in 15 days.

b. To reassure them, surely it is due to the lack of sports activity.

c. To indicate an iron and vitamin D supplement.

d. To request a full blood count and peripheral blood smear within 48 hours.

e. I refer him to Rheumatology.

11. With regards to retinoblastoma it is FALSE that:

a. It is the most frequent eye tumor in the pediatric age.

b. Strabismus is the most common presenting sign.

c. Up to 30% are bilateral.

d. Congenital cataracts can also cause leukocoria.

e. The prognosis will be better provided the disease is of isolated intraocular location.

12. A 12-year-old boy with abdominal pain accompanied by weight loss, asthenia, and sustained fever in the last week. On examination, a mass was observed on the right flank and the presence of intussusception was confirmed on ultrasound. Among the following options, which one would you suspect FIRST?

a. Wilms tumor.

b. Neuroblastoma

c. Urological malformation.

d. Non-Hodgkin lymphoma.

e. All are correct.

13. A 13-year-old boy attends our clinic referring a 2 month-course of localized pain in the right knee, which partially subsides with pain relievers, but does not go away completely. The child regularly plays soccer and remembers that, prior to the onset of pain, he hit that area. Lately, the pain prevents him from playing, he even has some limitation of joint mobility, he is very tired and has had fever for some days. On examination, he presents limited joint mobility with slight inflammation in the area, no other alterations. In this case our ATTITUDE should be:

a. Treatment with non-steroidal anti-inflammatory drugs for 1 week, with rest and clinical checkup in 15 days.

b. Reassure, it surely is a muscle overload following sports activity.

c. Referral to the Orthopedic surgeon for specialized evaluation, given the long course of the process.

d. Request anteroposterior and lateral x-rays of the area, as well as analysis with full blood count, peripheral blood smear, acute phase reactants and biochemistry with LDH and alkaline phosphatase within 48 hours.

e. Referral to Rheumatology for specialized assessment of joint discomfort.

Clinical case

14. In the case of the aforementioned patient, in the physical examination we must NOT forget:

a. Weight and height.

b. A complete neurological examination.
c. An ophthalmological examination where the pupillary response, visual acuity, ocular motility, fundus and visual field are evaluated.
d. Pubertal status.
e. All of the above are correct.

15. The Primary Care pediatrician is the professional who first assesses this patient. With the history and physical examination data, which one seems the most SUITABLE option?

a. Refer to the Ophthalmologist.
b. Make a clinical appointment in a week´s time, to monitor the course of the clinical picture.
c. Request a complete analysis.
d. Refer the patient to a specialized consultation within a maximum period of 48 hours, if an intracranial tumor is suspected.
e. Refer to a Neuropediatrician.

16. In a patient with suspected central nervous system tumor and signs of intracranial hypertension, which test would be indicated in the FIRST PLACE?

a. Urgent cranial CT scan.
b. Abdominal ultrasound.
c. Full blood count, biochemistry and clotting.
d. Chest X-ray.
e. Deferred brain MRI.