WHEN LYMPHOMA HIDES IN THE CANAL.

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Abstract

Primary intramedullary spinal cord lymphoma (PISCL) is a rare cause of myelopathies. As PISCL is often underrecognized, delaying appropriate treatment, we sought to describe its presentation. We report two clinical cases of pediatric patients. The diagnosis of PISCL must be considered in a patient with symptoms of acute myelopathies.

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Abstract

Primary intramedullary spinal cord lymphoma (PISCL) is a rare cause of myelopathies. As PISCL is often underrecognized, delaying appropriate treatment, we sought to describe its presentation. We report two clinical cases of pediatric patients. The diagnosis of PISCL must be considered in a patient with symptoms of acute myelopathies.

Key words : Primary intramedullary spinal cord lymphoma ,PISCL, Myelopathies, Chemotherapy.

CASE 1

Mattia is a 6-year-old boy with no previous medical history. He came for intermittent cramp-like abdominal pain in the last 48 hours, no fever, vomiting or diarrhea. Since some signs of inflammation in the appendix were found at an initial abdominal ultrasound scan, Mattia was sent to Pediatric Emergency Room (PER). Physical examination showed signs of acute abdomen. Therefore, he underwent a video-assisted trans-umbilical appendectomy with histological confirmation of acute appendicitis. After an initial clinical improvement, that allowed him to start walking independently on postoperative day four, we observed a progressive exacerbation of abdominal pain associated with difficulty in maintaining the sitting position.

The next day we also noticed an intermittent tenderness in the lower limbs and inability to keep the upright position and nocturnal enuresis. During a neuropsychiatric evaluation, the patient reported that he did not feel the urge to urinate and refused to leave autonomously the wheelchair. The neurological evaluation highlighted the presence of hypotonia and hyposthenia of the lower limbs, abolished patellar osteotendinous reflexes, abnormal plantar reflex in bilateral toe extension (Babinski sign). An electroneurography, a lumbar puncture and a magnetic resonance imaging (MRI) have been recommended to complete the diagnosis. The neurographic study showed only an asymmetry between left and right. Lumbar puncture showed elevated protein level (>700 mg/dl) in the cerebrospinal fluid, which supported the suspect of a Guillain-Barre syndrome (GBS). Therefore, a treatment with intravenous immunoglobulin at a dose of 0.5 g/kg/day was started. The following day the clinical picture of the patient appeared unchanged. An encephalic and spinal MRI was executed, showing an epidural intracanal tissue located from D7 to D11, associated with blurred signs of medullary suffering (Figure 1A and 1B).

An urgent surgical decompressive laminotomy on 5 levels was performed, with removal of most of the pathological tissue (Figure 1C and 1D). The histological examination reported a pre-B lymphoblastic lymphoma. Mattia has been subsequently transferred to the Onco-hematology department to undertake a specific chemotherapy treatment for the underlying disease. High-dose steroid therapy with methylprednisolone succinate was prescribed.

After surgery Mattia showed a persistent severe hypotonia in the lower limbs, absence of spontaneous movements with weak patellar and Achilles' osteotendinous reflexes and recovery of tactile sensitivity.

During the hospitalization, the initial paraparesis gradually improved thanks to a targeted rehabilitation program. Distal motor deficiency was associated with intestinal dysmotility, anal sphincter disfunction and spastic neurogenic bladder. The initial difficulty in perceiving the stimulus to defecate and the anal sphincter atony has progressively improved, until resolution. Neurogenic bladder, characterized by an increase in daily urinations with a small amount of urine and mintional urge, was treated by oxybutynin. Intermittent catheterizations were performed six times a day as prophylaxis of urinary tract infections. The patient was found to have 3 asymptomatic bacteriuria, from catheter urinary sample cultures, treated according to the antibiogram. Currently, the number of daily urinations has partially reduced and mintional urge has improved.

CASE 2

Luca is a 13-year-old boy admitted in the pediatric emergency room, complaining hypoesthesia of the lower limbs, with increasing difficulty in walking, during the last seven days.

About 25 days before, the boy reported difficulty in bending the head after physical activity (weight throw). Due to persistent pain, he underwent an orthopedic examination with cervical spine x-ray. The imaging showed vertebral instability characterized by moderate retrolisthesis of C3-C4 and C4-C5.

After a while, Luca began to complain paresthesiae of the lower limbs associated with walking difficulties. Taping was removed, with immediate benefit. After a few hours, however, paresthesiae and difficulties in walking appeared again. Child neuropsychiatric evaluation was then performed, but the neurological objective examination was negative.

After 48 hours the boy returned to the PER, complaining inability to walk, with no pain in the lower limbs. At the physical examination he was not able to keep the standing position. Lower limbs muscle contractions were

present intermittently for short intervals of time. These muscles had normal consistency with no tenderness to the palpation. Deep tendon reflex was present and symmetrical. No sphincter, nor sensitive deficits were detected. After confirming a worsening of the motor deficit, we decided for hospitalization.

On the following day, brain and spinal MRI were performed, with evidence of an expansive intravertebral epidural lesion in the dorsal area, extending from D1 to D3, which involves and widens the conjugation foramina of the left side (Figure 2A and 2B). Additionally, there was also another polylobed formation with similar characteristics in the right mid-thoracic area along the costal margin line.

The patient therefore underwent an urgent neurosurgical intervention of laminotomy and removal of the mass compressing the medulla (Figure 2 C and 2D).

Histological examination showed an anaplastic large-cell ALK-positive lymphoma. After surgery, the patient presented incomplete paraplegia. A specific chemotherapy protocol was undertaken, followed by a rehabilitative management, with the execution of daily exercise sessions.

After the first discharge from the department of Pediatric Oncohematology, following about 2 months of physiotherapy, Luca showed an initial motility of the lower limbs with the possibility of loading. Over time there has been a progressive improvement of the motor deficit, until complete resolution. At present, he usually plays tennis.

DISCUSSION

We report the unusual cases of two children with symptoms suggestive for acute myelopathy, who resulted both affected by Primary Intramedullary Spinal Cord Lymphoma (PISCL). Though considered rare spinal canal tumors, PISCL should always be included in the differential diagnosis of acute myelopathy, because any delay in diagnosis and treatment could significantly impact on the prognosis of this disease.

Among the oncological causes of compressive myelopathy in the pediatric population, non- Hodgkin lymphomas (LNH) are the main group. LNHs are represented by a heterogeneous group of malignant neoplasms of lymph node tissue derived from the progenitors or mature B lymphocyte cells or, with lower frequency, T lymphocyte cells. While in adult the predominant subtype is low-grade, clinically indolent, lymphomas in pediatric age are mainly high-grade and characterized by an aggressive behavior (1). Extra nodal location in LNH of the child-adolescent, which differs from that of the adult, is more frequent, with involvement of the mediastinum, abdomen, head-neck district, bone marrow or central nervous system (2). Symptoms often develop rapidly, over a period of 1-3 weeks (see Table 1 for signs and symptoms). The onset of lymphadenopathy, with lymph nodes increased in size and indolent, is common as well as compression symptoms on the surrounding structures.

Our two clinical cases emphasize how clinical presentation of LNH frequently constitutes a challenge for the pediatrician because of the variety of possible onset manifestations and the different types of lymphomas and areas involved. For example: a chronic, deep, dull abdominal pain, devoid of specificity and precise localization, can characterize the onset of a LNH with primitively medullary localization. The main cause of this clinical sign is the stimulation of the nerve endings present in the wall of the bowel by the neoplasia (see Table 2 for red flags of PISCL).

However, acute abdominal pain is frequently a diagnostic challenge in children due to the difficulty in correctly interpreting a nonspecific symptomatology. Acute paraplegia in children is also a rare clinical presentation of lymphoma, with signs and symptoms reflecting spinal cord dysfunction. The 4 main etiological groups (see Table 3) of motor paralysis and/or functional deficit of the lower limbs in pediatric age consist of:

1. trauma (for example, from falls or road accidents);
2. vascular pathologies, including epidural spinal hematoma, caused by the rupture of epidural veins in correspondence of a locus minoris resistentiae following a sudden increase in intrathoracic or intra-abdominal pressure, due to efforts (even when of low intensity such as cough or defecation);

3. inflammatory diseases (including primary infections, abscesses, polyradiculoneuropathy and infection associated processes, such as transverse myelitis and encephalomyelitis);
4. compressions (tumors, syringomyelia) (11-12).

According to an Australian case study, the most common cause of acute flaccid paralysis of the lower limbs (up to 47% of cases) is GBS (5).

Malignant compression of the spinal cord (MCSC), whether it is caused by a primary tumor localization or as the consequence of a metastasis, can be divided into two types, depending on location: extradural (the most frequent in adults, extending from the vertebral bodies or from structures external to the dura mater) and intramedullary (14). Despite their impact on morbidity and mortality, only a small amount of data on the incidence of the disease are available in the pediatric population. Acute spinal cord compression can occur in a not negligible percentage of children with cancer, often at the time of diagnosis (15). Tumors associated with medullary compression in childhood are shown on table 4.

In an italian case study in pediatric oncology, motor deficit was the onset symptom of MCSC in all patients, while pain was reported in 60% of cases and sphincter deficit in 43% (3). MRI is the diagnostic technique of choice in all cases when there is suspicion of medullary involvement (3). This exam should be carried out as soon as possible because the neurological prognosis is strongly related to the promptness of spinal cord decompression surgery (11). Complications of spinal cord compression, such as urinary dysfunction, fecal incontinence, spasticity, painful syndromes and psychological sequelae are complex problems for children and adolescents (13). According to the latest 2013 guidelines of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons, the use of glucocorticoids in acute traumatic spinal cord injury is no longer recommended.

The American Academy of Emergency Medicine states that glucocorticoid treatment remains an acceptable option. Many experts affirm that there are compelling and undeniable data justifying the clinical use of glucocorticoids, particularly in patients with incomplete lesions. The molecule to be used should be methylprednisolone, administered intravenously. The therapeutic scheme is:

30 mg/kg in bolus in 15 minutes

After 45', 5,4 mg/kg infused every hour for 23 hours. (18)

A bladder dysfunction can lead to difficulties in urination associated with changes in intravesical pressure, an increased risk of infection and kidney damage as well as a source of social distress. Urinary symptoms can be very variable, ranging from an increase in urinary frequency to a complete urinary retention. It is therefore mandatory to perform a proper neurological examination (complete with evaluation of sphincter function and reflexes), a mintional diary, to measure residual post-mintional volumes and to execute urodynamic studies. Similarly, the presence of neurogenic bowel can be a source of serious social distress and skin impairment. Laxatives or anti-diarrheal drugs with pelvic floor rehabilitation can improve sphincter control (14). On the other hand, several studies show how neurological recovery in childhood is better than in adulthood (6) thanks to the greater plasticity of the immature spinal cord (7-8). In a recent work, the presence of residual muscle activity in children, found in electromyography analysis of the motor sites located below the level of injury, documents the existence of a residual descending influence from the spinal motor circuits. This observation, independently of its immediate functional relevance, can represent an objective indicator of the potential recovery of both intentional and postural motor function (16). Physiotherapy, following damage to the spinal cord, is still one of the key processes in the rehabilitation of the patient (9-10). Age at the time of diagnosis, location and degree of spread of the spinal cord injury are the main prognostic factors for the recovery of gait. Children under 5 years of age, with incomplete injuries, located in thoracic or lumbar spine, have the best chance of functional recovery thanks to physiotherapy (17).

CONCLUSIONS

A child presenting recent gait alterations or motor impairment, whether or not associated with pain and sphincter deficit, especially if rapidly progressive, must be promptly evaluated in the hospital. Root pain

and motor impairment may be the first signs of spinal compression. The rapid onset and evolution of symptomatology have been an important warning signal.

It is essential to know the possible clinical manifestations of medullary compression in order to be able to recognize them and avoid unsuitable treatments for patients.

Authorship List

Conceptualization: Daniele Zama, Egidio Candela, Gennaro Pagano, Francesco Venturelli; data curation: Egidio Candela; formal analysis: Daniele Zama, Egidio Candela. Neuroradiological images: Francesco Toni; supervision: Fraia Melchionda, Mino Zucchelli, Andrea Pession; validation: Andrea Pession; visualization: Egidio Candela; writing – original draft: Egidio Candela, Gennaro Pagano, Francesco Venturelli; writing – review and editing: Daniele Zama, Fraia Melchionda, Mino Zucchelli, Andrea Pession. All the authors have read and agreed to the published version of the manuscript.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Statement of Ethics

Written informed consent was obtained from the patient for the publication of these case reports and any accompanying images. Ethics committee approval was not obtained because we report a clinical case of only two patients, we have not included any identifiable information, and we obtained written consent for publication from the patient's parents according to the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This retrospective review of patient data did not require ethical approval in accordance with local guidelines.

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Figures:

Figure 1. **Sagittal (A) and axial (B) T2 weighted images.** Pre-operative picture shows epidural vertebral canal tissue (arrow heads in A and asterisks in B), located from D7 to D11, slightly hyperintense to the medullary nervous tissue. The lesion compresses and dislocates the dural sac and its contents antero-laterally, towards the left (arrow in B), with extension, through the right conjugation foramen, into the adjacent costvertebral space (asterisk in A). An area of altered signal, expression of medullary suffering, at level D11-D12 (arrows in A) is associated.**Sagittal (C) and axial (D) T2 weighted images.** Post-operative picture after the removal of the neoformation, with resolution of the associated mass effect (arrowheads in C) and the area of medullary suffering. Noteworthy is the prompt response to chemotherapy of the extended component in the right costovertebral space. Figure 2. **Sagittal T2 weighted (A) and T1 weighted images after contrast administration(B).** Before surgery picture was characterized by intravertebral epidural neoformation, located in the D1-D3 tract (arrowheads in A and asterisks in B), characterized by a signal similar to the that from the spinal cord in T2, because of high cellularity, as well as by lower contrast impregnation (asterisks in B). The lesion described engages almost entirely the spinal canal, with a marked compressive effect on the dural sac and its contents (white arrows in A), dislocated laterally to the left (black arrow in B). The neoformation extends into the costovertebral adipose tissue through the intervertebral foramina, on the left side.**Sagittal (C) and axial (D) T2 weighted images.** Post-operative picture characterized by the removal of the lesion (arrowheads in C), with a reduction of the associated mass effect. On the post-operative phase, the spinal cord early appears distorted by previous compression (arrows in C and D), however, without radiological features of suffering.

Asymptomatic peripheral lymphadenopathy Medullary infiltration (lymphoma if the neoplastic medullary infiltrate is <25%

Table 1 : Main clinical manifestations of the LNH.

Radicular pain (cervical-brachial, abdominal, lumbar-cruralgia, lumbar-sciatalgia)
Hypoesthesia of the limbs (compression of the cervical cord can cause weakness
extended to the 4 limbs. The most frequent presentation is strength deficit at the lower limbs, usually symmetrical, but som
Progressive reduction of sensitivity
Sphincter dysfunction

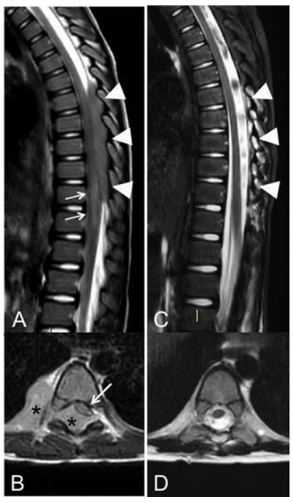
Table 2 : Red Flags of warning signs and symptoms for LNH with primarily medullary localization.

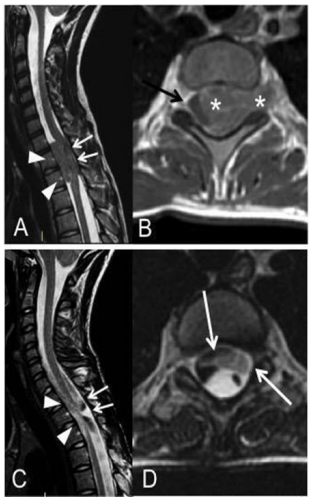
Congenital	**Genetic disorders**	**Acquired**
Spinal dysraphisms Arnold-Chiari malformation Skeletal Malformations	Hereditary spastic paraplegia Spino-cerebellar ataxia Adrenomyeloneuropathy Other leukodystrophies Spinal muscular atrophies	Traumas Degenerative disorders of the spine Metabolic pathologies Vascular pathologies Inflammatory diseases (transverse myelitis) Autoimmune diseases Infectious diseases Neoplastic diseases

Table 3 : Main causes of myelopathy in pediatric patients.

Neoplasms of the spinal cord Extradural Epidural	**Neoplasms of the spinal cord Extradural Osteo-cartilaginous**	**Neoplasms of the spinal cord Extradural Peri-vertebral**	**Neoplasms of the spinal cord Intradural Intramedullary**	**Neoplasms of the spinal cord Intradural Extramedullary**
Leukemia Lymphoma PNET Germ cell tumors Lipoma	Ewing's sarcoma Osteo-sarcoma Osteoid osteoma Osteoblastoma Langerhans cell histiocytosis Aneurismatic bone cysts Hemangioma Sacrococcygeal Teratoma Lymphoma Leukemia	Neuroblastoma Ganglioneuroma PNET	Astrocytoma Ependymoma Ganglioglioma Lipoma	Neurofibroma Schwannoma Meningioma Malignant peripheral nerve sheath tumors Myxopapillary ependymoma Dermoid/epidermoid cysts PNET Atypical Teratoid Rhabdoid Tumors Lipoma

Table 4: Main tumors that can cause spinal cord compression in childhood.





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