Subacute Trismus in a Kidney Transplant Recipient

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This case report describes a male patient with trismus and generalized muscle weakness as the presenting symptom of disseminated malignancy. Trismus was caused by the presence of multiple small nests of undifferentiated tumor cells between muscle fibers of the masseter muscles as well as of other skeletal muscles. The diagnosis was suggested by increased uptake of 18-fluoro-deoxyglucose on positron emission tomography and subsequent ultrasound examination. The primary tumor was not found on autopsy. The patient was at increased risk for malignancy due to his renal transplantation 16 years before. J OROFAC PAIN 2010;24:412–416

Key words: malignancy, positron emission tomography, transplantation, trismus, weakness

Trismus, the inability to normally open the mouth, is a potentially life-threatening condition and may cause permanent functional impairment. Infection (odontogenic and non-odontogenic), trauma, dental treatment, temporomandibular joint disorders, tumors, radiotherapy, certain drugs, congenital disorders, systemic diseases, central nervous system disorders, and miscellaneous problems are possible causes of trismus (see Table 1).[1–4] This article reports an unusual case of trismus caused by tumoral invasion of the masseter muscle, with a fatal outcome.

Case Report

A 68-year-old man, with a history of kidney transplantation for idiopathic chronic renal failure 16 years before, was admitted to the University Hospitals Leuven nephrology ward with progressive difficulties in opening his mouth and associated jaw pain. He also mentioned throat pain. Food intake was limited, but he reported no apparent recent weight loss. Over the previous 4 weeks, he also developed diffuse pain in the musculoskeletal system, more specifically in the shoulder, elbow, and knee joints as well as in the lumbar spine. In contrast, wrists, hands, and feet were not involved. He indicated general weakness and stiffness developing over several weeks. Fever and chills were absent. There was no history of recent infection, trauma, or dental procedures.

In addition to the kidney transplantation, his medical history included ischemic heart disease and surgical repair of an abdominal aortic aneurysm 3 years earlier, complicated with multiple organ failure and prolonged stay in an intensive-care unit. After recovery, physical activity remained somewhat limited. At admission, he was taking

Table 1 Causes of Trismus[1-4]	
Infection	
Odontogenic	Pulpal, periodontal, pericoronal [13]
Nonodontogenic	Peritonsillar abscess[14] parotid abscess, submasseteric abscess,[15] infratemporal bone abscess, meningitis,[16] encephalitis,[17] tetanus[18]
Trauma	Fracture of the mandible,[19] zygomatic arch,[20] skull base, foreign body,[21] traumatic myositis ossificans,[22-24] muscle fibrosis posttrauma/burns/surgery[24]
Dental treatment related	Inflammation of muscles of mastication following extraction of wisdom tooth, needle tract infection, or foreign body reaction following mandibular nerve block, hematoma with fibrosis after mandibular nerve block, muscle scar tissue after surgical muscle dissection[25,26]
Temporomandibular joint disorder	
Extracapsular	Myofascial pain[27]
Intracapsular	Rheumatoid arthritis, septic arthritis,[28] osteoarthritis, fibrosis, articular disc displacements without reduction[29,30]
Tumors (primary or metastatic)	Invasion of the masticatory space, the ascending ramus of the mandible or temporomandibular joint, or precancerous condition (submucosal fibrosis)[31–33]
Drugs	Phenothiazine, succinyl choline, tricyclic antidepressant, metoclopramide,[34] halothane
Radiotherapy	Postradiation fibrosis, osteoradionecrosis[35]
Congenital	Hypertrophy of the coronoid proces, trismus-pseudocamptodactyly syndrome[36]
Systemic diseases	Lupus erythematosus,[37] scleroderma, giant cell arteritis[38]
Central nervous system disorders	Cerebrovascular accident,[39] multiple sclerosis,[40] vascular compression of the trigeminal nerve[41]
Miscellaneous	Hysteria,[42] Gaucher disease[43]

the following medications: cyclosporine (125 mg/d), methylprednisolone (4 mg/d), acetylsalicylic acid (80mg/d), amiodarone (200 mg/d), antihypertensives (nifedipine 60mg/d, nebivolol 5mg/d), pantoprazole (40mg/d), and simvastatine (20mg/d). Prior to the admission, he had seen a stomatologist who suspected arthritis of the temporomandibular joint and started treatment with ibuprofen, which did not bring relief.

Clinical Examination

On initial clinical examination, mouth opening was limited to 8 mm and associated with remarkable pain elicited at the temporomandibular joint when the examiner applied finger pressure to the joint. Diffuse submandibular and submental painful swelling were present. Cervical and submandibular lymph nodes were not enlarged. Although hindered by the limited mouth opening, examination of the teeth, oral cavity, and throat did not show oral and laryngeal lesions. Tonsils could not be evaluated due to the limited mouth opening.

The rheumatological examination showed tenderness to palpation of the temporomandibular joint regions but no clear joint swelling. There were no clinical signs of arthritis in the other joints, except in the elbow where some swelling was noticed. Ultrasound of the elbow showed a limited amount of fluid in the right elbow joint and thickening of the flexor muscles with the presence of nodular structures. The lumbar region and quadriceps muscles were very sensitive to finger pressure applied to the region.

Finally, cardiopulmonary and abdominal evaluation was unremarkable.

Blood Tests

Initial laboratory tests showed a white blood cell count of 8×10^9/l (69% neutrophils), a slight increase in C-reactive protein (14.2 mg/l) , creatinine (1.60 mg/dl), and lactate dehydrogenase (529 U/L). Erythrocyte sedimentation rate was normal. X-ray of the jaws was also normal. Rheumatoid factor, anticyclic citrullinated protein antibodies, antinuclear factor, and antineutrophil cytoplasmic antigen antibodies were absent.

Initial Differential Diagnosis

A clinical diagnosis of trismus was made. Based on the history, the authors could eliminate trauma, dental treatment related causes, radiotherapy, and drugs known to be possibly associated with trismus as causal factors. Initial findings were not consid-

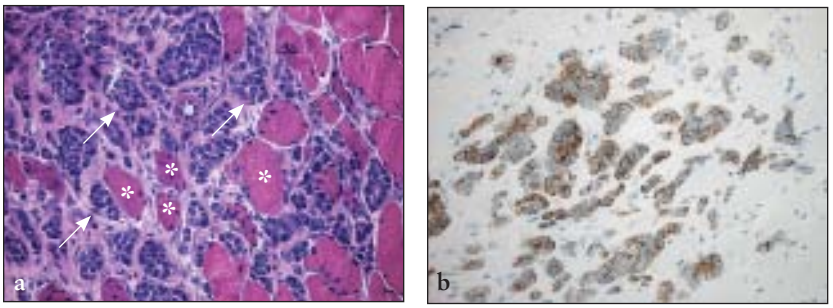

Fig 1 Histopathology of the quadriceps muscle. *(a)* hematoxylin & eosin stain, showing the tumoral cell nests *(arrows)* in between the muscle fibers *(asterisks)*, ×400; *(b)* the tumor cells were strongly positive for keratin (immunohistochemistry, ×400).

ered to be due to hysteria and, because of the patient's age and lack of other associated signs, such as distal arthrogryposes, congenital causes could also be excluded. As clinical evaluation of the oral cavity was limited, a computed tomography (CT) scan was performed to rule out collections as well as tumor masses in the tonsillar region and masticatory space. This did not reveal any abnormalities, although the quality of the images was negatively influenced by the presence of silver amalgams in different teeth. At this stage, a dental, oral, or submandibular cause appeared unlikely. Concerning distant infections, at least typical bacterial meningitis and encephalitis could be excluded as the C-reactive protein level was low, the patients' consciousness was absolutely normal, with absence of headache and signs of meningeal irration, although the immunosuppressive status did warrant caution concerning smouldering infections such as tuberculosis. *Clostridium tetani* infection was also excluded as there were no other signs of tetanus, such as stiffness in the neck, reflex irritability, and autonomic hyperactivity as well as no history of a recent wound.

To rule out rare central neural causes of trismus, such as stroke, brain imaging with CT scans and magnetic resonance imaging (MRI) was performed and did not reveal any causative factor.

The clinical picture with marked musculoskeletal pain, including the shoulder and hip regions, and some inflammation could have pointed to polymyalgia rheumatica, a common inflammatory disease in elderly patients. However, the likelihood of polymyalgia, as well as other systemic diseases such as lupus or scleroderma, was limited, as the patient was treated with strong immune-suppressive drugs, and sedimentation rate was normal as well as autoimmune screening. Arteria temporalis biopsy was still performed, which was normal.

There was no history of clicking or acute closed-lock. However, palpation of both temporomandibular joints was painful, as were the submandibular and submental regions and the upper and lower limbs. Limb muscle force upon formal evaluation was considered to be submaximal (4/5), and diffuse hyporeflexia was present.

At this stage, the patient's condition worsened.

Follow-up and Definitive Diagnosis

Seven days after admission to the hospital, the patient developed pneumonia, and treatment with piperacilline-tazobactam was started. Within 48 hours, the patient was transferred to the intensive-care unit because of respiratory failure necessitating intubation and mechanical ventilation. The patient was intubated orally after administration of a neuromuscular blocking agent (cistracurium), which only led to a slight mouth opening increase. Careful inspection of the teeth and oral cavity by a stomatologist after intubation showed teeth that were well taken care of and a normal mucosa. Some signs of bruxism were apparent on the teeth, which the stomatologist considered not responsible for the trismus. At this time, the most likely diagnosis appeared to be a general myopathy, which could be paraneoplastic as this patient was at increased risk for neoplastic disorders due to the immunocompromised state. Also, indolent infectious cause was still being considered. For this reason, a positron emission tomography (PET) examination using 18-fluorodeoxyglucose was performed, which would be able to identify tumoral as well as infectious lesions. The PET showed hot spots in the right supraclavicular and axillar region, as well as diffuse 18-fluorodeoxyglucose-uptake in both lungs and all muscles. These images suggested the presence of widespread infection or malignancy.

Subsequently, ultrasound of the supraclavicular and axillary region was performed and showed

small, hypodense nodules in the infraclavicular and axillary muscles, as well as in the masseter muscles. Biopsy of the quadriceps muscle was obtained, and histomorphological analysis revealed tumor cell nodules in between muscle fibers (Fig 1). The undifferentiated tumor cells showed hyperchromatic atypical nuclei and only scant cytoplasm. On immunohistochemistry, the leucocyte markers CD3, CD 20, and CD 45 were negative, while keratin staining was positive. Chromogranin and CD 99 were negative. A final diagnosis of disseminated poorly differentiated carcinoma of unknown origin was established. The further course of disease was complicated with pulmonary edema and progressive renal failure. The poor prognosis led to a joint decision to discontinue therapeutic interventions, and the patient died 11 days after intensive-care unit admission.

Discussion

This paper has described a case of poorly differentiated carcinoma of unknown origin in an immunosuppressed host with subacute trismus and general weakness as presenting symptoms.

The presence of multiple hypodense nodules in all muscles, including the masseter muscles, suggested the diagnosis. The case showed that the differential diagnosis of trismus can be complex as several pathologies, both local or systemic, can cause it.

Malignancy is a known cause of trismus. Tumors can directly invade the masticatory muscles or can cause trismus by invasion of the mandibular trigeminal nerve branch. Perineural spread of tumor in the neck and head is not uncommon and may be the revealing sign of cancer. Most commonly, this is caused by squamous cell carcinoma[5] and by adenoid cystic carcinoma.[6] Direct tumoral invasion of the muscle is most commonly seen in patients with metastasis,[7] as in this case, but also by a direct ingrowth for tumors, such as the adenoid cystic carcinoma.[8]

The patient's immune suppression after kidney transplantation may have contributed to the insidious progression of the malignancy. The most common malignancies encountered in the posttransplant setting are nonmelanoma skin cancers, posttransplant lymphoproliferative disorders, and Kaposi's sarcoma.[9] Others, including non-Kaposi's sarcomas and gastrointestinal, urogenital, and thoracic tumors, have also been reported.[10] Malignancies occur in up to 40% of patients 20 years after renal transplantation, compared with a 6% cumulative risk in age-matched, nontransplanted controls.[11] Malignancy is the reported cause of death in up to 26% of kidney transplant recipients who survive for at least 10 years.[12]

Trismus can have serious health implications, including reduced nutritional intake, difficulty in speaking, and compromised oral hygiene. The causal factor should be actively searched. As the deeper parts of the masticatory space are difficult to evaluate by clinical examination, imaging using CT and/or MRI is part of the diagnostic work-up. In this patient, the cause was only found after the PET examination, followed by selective ultrasound examination.

In summary, this case report highlights the challenges in the diagnosis of trismus, particularly in patients with complex medical histories and problems.

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