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Case Report

Palliative Care: Multidimensional Challenges in Patients with Severe Chronic Illness

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Abstract

Palliative medicine provides symptomatic care to patients suffering from serious chronic illnesses and offers psychological support to both patients and their families. Palliative care has been historically the main or only therapy assigned to patients with advanced cancer. In the present, palliative care has become an important adjuvant in cancer care along the long trajectory of disease management. Symptomatic long-term palliative care has its place in the management of advanced heart failure, respiratory failure, liver failure, renal failure and multi organ failure. Even in the most limited sense palliative care is demanding. Yet, caring for patients with severe chronic diseases, involves challenges beyond the strict discipline of palliative medicine. Consideration is needed for the gamut of problems for which the general physician might not be prepared or skilled, and which might require expert consultation and expert management. The complexity and variety of situations faced by physicians in palliative/hospice care is illustrated by ten case histories presented in the following. Palliative care is never simple. It is often propelled by multidimensional challenges.

Keywords: Cancer; Hospice Care; Palliative Medicine

Introduction

By definition palliative care provides symptomatic care and psychological support to patients suffering from serious chronic illnesses. Palliative care is no longer synonymous with end of life care, rather in many cases palliative care is instituted together with curative interventions during the course of severe chronic diseases. This shift in the implementation of palliative care has been largely acknowledged [1,2]. Palliative care is indicated for patients with cancer and, also, for persons suffering from advanced heart failure, respiratory failure, liver failure, renal failure, multi organ failure or chronic pain syndromes. A variety of symptoms is addressed during palliative care, and comprise pain, shortness of breath, delirium, depression, insomnia, nausea, vomiting, constipation, and pruritus.

The term hospice care is used to describe a specific model of palliative care offered to patients who are at the end of life with terminal disease, when curative or life-prolonging therapy no longer provides the focus of treatment. Yet, even in the extreme situation of patients assigned to hospice care, end of life is not necessarily imminent. Under the same diagnosis, the same disease, and with similar prognosis according to guidelines, the course of the patients' disease may differ. Hence, treatment should be tailored according to the patient's factual condition, which may be consistent or inconsistent with statistical data provided by evidence-based medicine.

Meeting the goals of palliative care, in their limited sense, is demanding, yet many other challenges can present. The variety of problems faced by physicians at the bedside is illustrated in case histories from our recent experience. The challenges were so very different and comprised paraneoplastic postural hypotension, brittle diabetes mellitus secondary to pancreatectomy, central diabetes insipidus, feeding intolerance, drug-induced tardive dyskinesia, sepsis associated encephalopathy, and priapism. Awareness and consideration are warranted in coping with problems outside the strict discipline of palliative medicine. Expert consultation and expert management might be required. In practice, palliative care is never simple and often complicated by multidimensional challenges.

Case Histories

Case 1: Post-pancreatectomy postural hypotension and brittle diabetes mellitus. A 74-year-old woman diagnosed with adenocarcinoma of the head of the pancreas underwent total pancreatectomy, splenectomy and gastrectomy with Roux-en-Y esophago-enterostomy. Metastases to the omentum were present. She received chemotherapy according to the FOLFOX protocol. Diabetes mellitus developed after pancreatectomy. She was treated with insulin glargine and insulin glulisine as well as high dose of oral pancreatin. Though PET- CT showed no evidence of remnant disease, the patient was weak and fainted several times. Her blood sugar was difficult to control with repeated episodes of hypoglycemia. Soon it became apparent that the patient had severe orthostatic hypotension. The onset of postural symptoms was recent, and her family physician and oncologist were unaware of hypotension. During postural challenge (Figure 1) there was severe decrease of the blood pressure without compensatory tachycardia - a finding consistent with neurogenic orthostatic hypotension. Diabetic autonomic neuropathy or paraneoplastic autonomic neuropathy were considered among the possible causes [3,4].

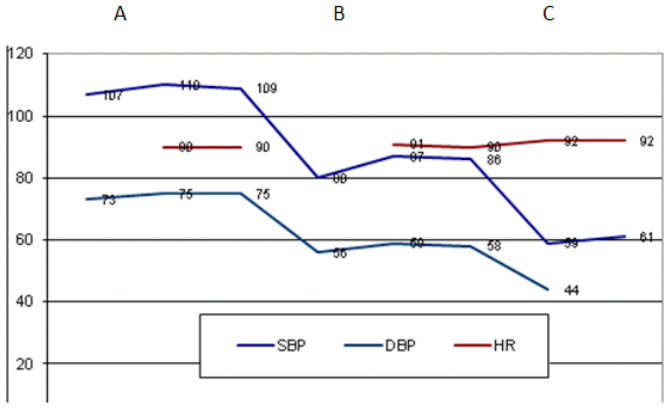

Figure 1: Bedside postural testing with the patient wearing elastic bandages on her calves and thighs. A significant decrease in blood pressure is noticed on assuming the seated position, and a brisk further decline upon standing, necessitating immediate termination of the test. A: supine, B: sitting, C: standing.

Treatment of postural hypotension was initiated with a high salt diet combined with the vasoconstrictor midodrine (titrated to 20 mg/day) and fludrocortisone 0.2 mg/day. Good control of hypotension was achieved (Figure 2) without further use of elastic bandages.

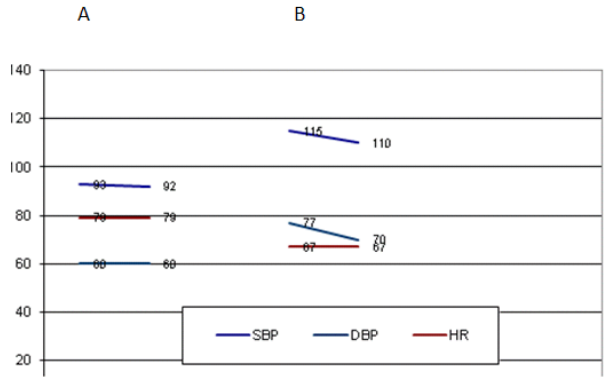

Figure 2: Blood pressure and heart rate under treatment. A: supine measurements before intake of medications, B: after intake of midodrine and fludrocortisone measurements in sitting position in postprandial state.

More difficult to control was the post-pancreatectomy diabetes mellitus. Diabetes mellitus secondary to total pancreatectomy, which is insulin dependent like type I diabetes mellitus, however, differs very much from type I diabetes. Patients with total pancreatectomy lack not only insulin, but also glucagon, the counter regulatory hormone to insulin and therefore are prone more to hypoglycemia under insulin treatment [5]. In a study comparing the two conditions, the basal insulin in total pancreatectomy was as low as 3.7 units/day, which was less than one - third the dose required in type 1 diabetes. The prandial insulin dose of insulin was similar. Brittle diabetes after total pancreatectomy is best treated by continuous insulin delivery [6].

During the 5-month hospitalization in our ward the patient lost 1 kg in weight but felt better. Postural hypotension is controlled. Glycemia is difficult to control but there were no hypoglycemic events. Further courses of FOLFOX treatment have been scheduled.

Case 2: Cholangiocarcinoma - complications of disease and complications of treatment A 76-year-old woman was admitted for post-acute care having recovered after a minor stroke. Until recently she had been mentally and physically well, having just returned from the Far East. But her medical history was laden with disease: cholangiocarcinoma diagnosed in 2015, four years prior to the current admission. There had been remission of the symptoms after resection of left hepatic lobe followed by chemotherapy. When the disease recurred in 2017 fluoropyrimidine-based Selective Internal Radiation Therapy (SIRT) with yttrium-90 resin microspheres was

provided. In 2018 low-SAAG ascites occurred needing repeated large volume paracentesis. The patient's history comprised type 2 diabetes mellitus, that recently had become difficult to control, and peripheral neuropathy that might have been a complication of the diabetes or chemotherapy. On admission to our ward the blood pressure was 112/56 mmHg. The abdomen was distended with shifting dullness. The hemoglobin was 7.2 g/dL, platelets 65000/mm^3, serum albumin 2.6 g/dL, eGFR 71 ml/min/1.73m^2 (within normal range). The patient's daily medication comprised spironolactone 100 mg, furosemide 40 mg, insulin glargine 30 U, postprandial insulin glulisine, metformin 1700 mg and 800 U vitamin D3. To avoid tense ascites, paracentesis was performed at 14-day intervals, removing 3.5 - 4 litre of fluid, without the need for i.v. albumin replacement. Subsequently, episodes of delirium occurred, rising suspicion of hepatic encephalopathy. The presence of high serum ammonia supported the diagnosis. Treatment with lactulose and rifaximin was beneficial.

When frequent vomiting intervened, the cause remaining obscure, metoclopramide 5 to 10 mg was administered as needed. Vomiting subsided after two weeks and metoclopramide was discontinued. However, there was neurologic deterioration manifesting as dyskinesia and delirium. Stereotypic movements of the mouth, tongue twisting and protrusion, grimacing, writhing movements of the trunk and choreoathetosis movements of the fingers were observed. Tardive dyskinesia was diagnosed, possibly metoclopramide-induced, though the exposure to the drug was short and the dose small, not exceeding current recommendations [7]. Beside metoclopramide, other causes of dyskinesia were excluded on cerebral CT and cerebrospinal fluid examination.

Tardive dyskinesia is an involuntary movement disorder caused by chronic exposure to dopamine receptor antagonists and resulting in the upregulation of the dopamine receptors in the basal ganglia and damage to striatal cholinergic neurons. Tardive dyskinesia occurs most frequently after prolonged treatment with dopamine antagonists, particularly antipsychotic drugs or metoclopramide [7]. Therefore, it is currently recommended that metoclopramide treatment should not exceed 3 months. However, tardive dyskinesia occasionally occurs after short-term low-dose metoclopramide treatment [8], similar to the adverse reaction observed in our patient. After discontinuation of the drug symptoms of tardive dyskinesia can take months to resolve or may be irreversible. Currently it is possible to successfully manage this condition with other agents approved by the US Food and Drug Administration. Our patient was treated with biperiden and later sulpiride [9]. Improvement was witnessed after 2 months of combined treatment, the patient being able to eat and drink, but dyskinesia remained prominent 6 months after its onset.

This patient presented with numerous complications of the disease and treatment, and needed multi-disciplinary diagnostics and management. The diagnoses included SIRT-induced liver fibrosis, portal hypertension, ascites, portal vein thrombosis, hepatic encephalopathy, hepato-renal syndrome and metoclopramide-induced tardive dyskinesia. Six months after her admission to our ward the patient's condition remains stable at a very low level of function, necessitating continuing comprehensive nursing and medical care. There is no evidence of recurrence of the malignant neoplasm.

Case 3: Cholangiocarcinoma, feeding intolerance, entero-cutaneous fistula, fluid-electrolyte imbalance A 68-year-old man was admitted for supportive care between courses of FOLFIRI regimen (consisting of Folinic Acid (Leucovorin)-Fluorouracil-Irinotecan) for metastatic cholangiocarcinoma. Four years earlier he underwent left lobe hepatectomy followed by chemotherapy. Remissions and recurrences alternated. Lately, an entero-cutaneous fistula emerged draining 2 to 3 liters of turbid fluid. High dose loperamide was administered. By increasing the transit time of the intestinal contents loperamide reduces fecal volume and decreases the loss of electrolytes and fluids. In this patient, loperamide was of no avail.

Feeding intolerance became a problem and was initially attributed to impaired gastric emptying. A gastro-duodenal stent was inserted. However, the patient continued to feel discomfort after ingestion of food, suffered nausea and regurgitated or vomited. Feeding intolerance may be caused by gastrointestinal disorders, visceral pain, sepsis, chemotherapy (by affecting the cerebral chemoreceptor trigger zone), increased intracerebral pressure, gastric obstruction or gastroparesis. In the propositus, CT showed no obstruction and documented normal gastric emptying. First line treatment with metoclopramide for functional feeding intolerance was instituted but proved disappointing. Indeed, feeding intolerance constitutes an unmet therapeutic challenge [10].

Parenteral nutrition (1700 ml) was instituted. Aggressive correction of hypovolemia and electrolyte loss was provided as recommended for high output fistulas [11]. Dehydration was prevented by replacing fluid losses. Monitoring the volemia and diagnosing dehydration is not as simple as it might seem. No single clinical or laboratory parameter is satisfactory in diagnosing dehydration, neither serum osmolality, hematocrit, serum sodium, nor the BUN: creatinine ratio. Useful is the daily examination of the patient by the same physician, daily assessment of the fluid balance, with conventional 'laboratory markers of dehydration' serving as corroboration [12]. In adhering to this rule, the nutrition, fluid and electrolyte status of the patient was appropriate while he continued receiving chemotherapy.

Case 4: Sepsis-associated encephalopathy A 78-year-old man was transferred to our institution for long-term nursing care and life support. Until recently he had been fit and in good cognitive state until recently, with reasonably controlled arterial hypertension and diabetes mellitus. Having suffered a non-traumatic cerebral hemorrhage, mechanical ventilation was instituted, a subdural hematoma was drained and a ventriculoperitoneal shunt was inserted. Within a couple of weeks, the patient recovered from the

vegetative state. At the time of admission to our ward he was in stable hemodynamic condition, following tracheostomy and enteral feeding, alert but unable to undergo the mini-mental state examination. The medications comprised insulin glulisine and glargine, amlodipine, carbidopa-levodopa and vitamin D. During two-years of care in our department the patient suffered from repeated infections: urinary tract infections, epididymitis, pressure sores complicated by osteomyelitis, and pneumonias. Each event was heralded by lethargy; the temperature rose to 38.2-38.8 and the white blood cells up to 12.000/mm^3. As a rule, antibiotic treatment was started within 4 hours of onset of the symptoms. All incident infections were associated with neurocognitive decline, sometimes as low as the minimal conscious state, variably lasting 7-20 days. Recovery from infection was followed by improvement of cognition. The serum sodium, potassium, calcium, magnesium, thyrotropin, folate and vitamin B12 levels remained within the normal range. On cerebral CT no new lesions were noted, and the ventriculoperitoneal shunt was functioning. Sepsis-associated encephalopathy was the likely diagnosis. Sepsis-associated encephalopathy is a diffuse brain dysfunction secondary to infection outside the central nervous system. It is mediated by pathogen-associated molecular patterns and inflammatory cytokines which affect neurotransmission, impair mitochondrial and endothelial function, and damage brain-cells. Sepsis-associated encephalopathy manifests with acute alterations in memory, attention and concentration, that usually improve after remission of the infection. No treatment for sepsis-associated encephalopathy has proven efficacy [13,14].

The patient's cognitive state was fluctuated under the effect of infection; improvement after the remission of infection was sometimes delayed and incomplete. With cognition at its lowest point, a minimal consciousness state + was diagnosed: the patient's sleep-wake cycle was preserved along with comprehension of basic language. Emergence was apparent when the patient became functionally able to communicate and use objects [15]. Over a two-year period, repeated infections apparently had a cumulative negative effect on the patient's cognition. While sepsis-associated encephalopathy is usually transient and self-limited, under repeated or persistent systemic inflammation the cognitive and behavioural changes may become permanent [16].

Diagnosing sepsis-associated encephalopathy is challenging, especially with a background of chronic illnesses. Fever may be absent in frail elderly persons along with paucity of other signs of infection [17]; therefor, infection should be considered in the presence of new or increasing confusion, incontinence, falling, deteriorating mobility, reduced food intake, or failure to cooperate. Furthermore, a patient being treated with glucocorticoids when contracting an infection may have a blunted febrile response. Exclusions before diagnosing sepsis-associated encephalopathy should include hepatic, uremic, or respiratory encephalopathy, metabolic disturbances, drug overdose, withdrawal of sedatives or opioids, alcohol withdrawal delirium, Wernicke's encephalopathy and a variety of central nervous system disorders. Brain imaging may aid in the differential diagnosis.

Diagnosing and treating sepsis-associated encephalopathy are equally challenging. Most treatment schemes are geared toward treating the symptoms of delirium. None of the therapies that aim to treat the pathophysiological mechanisms of sepsis-associated encephalopathy have been proven effective in humans. It is reasonable, yet unproven, to presume that early initiation of antibiotic treatment might benefit cognitive recovery.

Case 5: The Post Intensive Care Syndrome (PICS) A 62-year-old woman was admitted for post-acute care after cardiac surgery. Until recently she had been living independently in the community. Her medical history comprised congestive heart failure, severe mitral and aortic regurgitation, pulmonary hypertension chronic atrial fibrillation, and type 2 diabetes mellitus. After open heart surgery - replacement of the mitral and tricuspid valves and closure of the left atrial appendage - the hospital course was complicated by pneumonia, sternal osteomyelitis, difficult weaning from mechanical ventilation and neurocognitive impairment. On admission to our institution she was mechanically ventilated. Her medications were TMP\SMX (160/800 mg), warfarin, bisoprolol, escitalopram, clonazepam, sildenafil, vitamin D and calcium gluconate, transcutaneous fentanyl, and inhalations with ipratropium. The prominent challenges in the management of this patient were delirium, severe cognitive impairment, stance and gait disorder, difficult weaning from mechanical ventilation and problematic control of warfarin treatment. Her consciousness was impaired, she was often apathetic, attention was easily distracted; at times she was agitated with delusions. During lucid intervals, the mini mental test scored MMSE 17/30, MOCA 13 (normal >24), clock drawing 3/5. Her stance was unsteady. She was able to take but a few steps using a walker and under supervision.

Among causes of the patient's neurocognitive deterioration, stroke, encephalitis and head trauma were excluded. Delirium is a common feature of subdural hematoma and may be mistakenly ascribed to infection or medication. A fall without head injury may account for up to 54 per cent of patients with subdural hematoma and there may be a long delay between a fall or trauma and the onset of the symptoms (range 15 to 751 days) [18]. The patient, being on warfarin treatment, was at increased the risk for subdural hematoma [19]. For these concerns a repeat cerebral CT was performed which excluded subdural as well as cerebral bleeding.

Medication is often the cause of delirium, particularly anxiolytics (the patient received escitalopram and clonazepam), antidepressants, opioids (the patient was treated with transdermal fentanyl), antiparkinsonians, antiepileptics, cardiovascular medications, antihistamines, corticosteroids, sedative-hypnotics, and drugs of abuse (alcohol, cannabis, cocaine). Considerable resources are sometimes expended before a newly administered drug is recognized as the cause of the delirium [20]. Trimethoprim–Sulfamethoxazole (TMX/SMX), which the patient was receiving, can cause various adverse neurologic events: aseptic meningitis,

delirium and gait disturbances. Neurologic symptoms that occur within days of continuous treatment usually resolve following discontinuation of TMX/SMX. We discontinued TMX/SMX, but no improvement of cognition, stance and delirium was witnessed. Six weeks later, in another sequence of events, TMP/SMX treatment was reinstituted; there were no deleterious consequences, on the contrary, cognition and stance were improving at this time and the patient was free of delirium.

It is not clear how long delirium lasts [21,22]. A study of patients suffering from delirium while hospitalized in a general medical ward found that in 70% of the cases delirium resolved by day 7. In another study, including elderly patients with delirium after hip fractures in 75% of the cases the delirium resolved by day 5. Delirium affects up to three quarters of patients after cardiac and non-cardiac surgery. Although delirium may resolve during hospitalization, delirium may have long-term functional and cognitive consequences. Since patients with postoperative delirium continue to have improvements in cognitive function up to 6 months after surgery, rehabilitation services may need to be extended for these patients [21].

Cognitive impairment after critical illness is very common and, in some patients, persists longer than a year. The Post-Intensive Care Syndrome (PICS) is diagnosed as a new or worsening function after critical illness affecting one or several of the following domains: cognition, psychiatric function, physical function. The memory and executive function are the most often affected domains, and often hinder a person from engaging in goal-directed behaviours that are necessary in effective daily functioning. Other common symptoms are weakness, poor mobility, poor concentration, fatigue, anxiety, and depressed mood. Commonly cited risk factors for the development of PICS are pre-existing illnesses (neuromuscular disorders, dementia, psychiatric illness) as well as ICU-specific factors (mechanical ventilation, delirium, sepsis, acute respiratory distress syndrome). The signs and symptoms of PICS improve modestly over the first 6 to 12 months following discharge from the ICU. However, in many patients, deficits persist for years. The effect of preventive or therapeutic interventions on PICS outcome is unknown [22]. PICS-family is the term used when critical illness of a loved one adversely affects the mental health of family members.

This patient recovered cognitively, her stance and gait improved, being weaned from mechanical ventilation and discharged home only eight months after cardiac surgery. Though PICS is not a new entity, it is not listed among the etiologies of acute onset dementias. PICS deserves awareness as well as long time rehabilitation.

Case 6: Lasting oral dysphagia and pressure ulcer after stroke A 58-year-old man was admitted to our ward with a large stage 4 pressure ulcer on the right heel. Adjacent to the pressure ulcer calcaneal osteomyelitis had been diagnosed. Before referral to our ward he had completed 6 weeks of antibiotic treatment. The patient's medical history included morbid obesity (his usual body weight was 140 kg, height 178 cm), type 2 diabetes mellitus, arterial hypertension and hypercholesterolemia. Two years before admission he had an ischemic stroke with right hemiplegia and aphasia. Thereupon, he had difficulty in swallowing and lost weight. He was unable to swallow the medications prescribed, including bisoprolol fumarate, enalapril, aspirin, glucosamine and omeprazole. On admission to our ward he was alert and communicated non-verbally. He was manifestly wasted. The present body weight was 67 kg. The body temperature, blood pressure and SpO_2 were normal. The body temperature, the previously elevated leukocyte and C reactive protein had returned to normal. He had facial weakness, delayed initiation of swallowing, piecemeal swallows and oral spill. Repeated trials to swallow were needed for satisfactory clearance of the ingested food (Figure 3). Cough sometimes followed. These features were consistent with oral dysphagia. A structural cause of oral dysphagia could be excluded by CT and fiberoptic endoscopy, such as Zenker's diverticulum, a neoplasm, osteophytes and cervical web. Signs of generalized muscle weakness were absent. Cerebral CT showed numerous old infarctions and severe cerebral atrophy. In the context of stroke preceding the dysphagia, the diagnosis of oral neurogenic functional dysphagia was proposed.

Figure 3: The patient's concentration is visible during attempts to propel the bolus within the mouth. A snapshot of the plate taken thirty minutes after beginning the meal shows little progress.

Normal swallowing necessitates the coordinated, synergic and progressive action of the lingual and pharyngeal muscles. The movements of the tongue upward and backward propel the bolus into the pharynx under volitional control. Hemispheric strokes may disrupt the control of oral bolus preparation and propulsion [23]. Dysphagia is a common problem after stroke. In many cases, dysphagia resolves quickly, but in others dysphagia persists. Dysphagia rehabilitation comprises manipulation of the food consistency along with techniques aimed to improve the strength and coordination of the orofacial musculature [24,25]. Helpful techniques are the chin tuck, head turn, Mendelsohn's maneuver and tongue

strengthening exercises. In the present case, though rehabilitation was started late, the swallowing improved remarkably. Though piece meal swallowing persisted, propelling the food became efficient the patient finishing the meals in 5 out of 6 instances. There was neither aspiration nor nasal regurgitation. He gained weight from 67 kg on admission to 92 kg after 14 months. The serum albumin increased to 3.8 g/dL. In parallel, over a period of 3 months the pressure ulcer healed.

Insufficient dietary intake is among the key risk factors for the development of pressure ulcers and delayed wound healing [26] and, probably, was a major contributor to impaired wound healing in this patient. Unless patients can swallow, enteral or parenteral nutrition is required to prevent an energy deficit that rapidly leads to wasting and pressure injury [27]. Malnutrition should be corrected and nutritional markers, such as albumin and prealbumin, be followed. When the patient becomes able to swallow, high-protein oral supplements are effective in reducing the incidence of pressure ulcers [28]. The American College of Physicians recommends protein or amino acid supplementation in patients with pressure ulcers [29]. Usually, patients with stage III and IV pressure ulcers should receive at least 30 kcal/kg/day to promote wound healing. Increased dietary protein intake also fosters healing of pressure ulcers. The protein target typically is 1.5 g/kg/day. Specific amino acids such as arginine, glutamine, and β-hydroxy β-methylbutyrate can be added to oral/enteral foods to accelerate healing [30]. Abound ®, a nutritional supplement containing arginine, glutamine and beta-Hydroxy Beta-Methylbutiric Acid (HMB), has been claimed to improve wound healing: the recommended dose is arginine 3 - 4.5g/day. However, evidence still remains inadequate to support the role of these agents in prevention or healing pressure ulcers [28]. Contrasting with this data, a 2014 Cochrane review found no clear evidence that dietary supplementation reduces the number of people who develop pressure ulcers or help the healing of existing pressure ulcers [29]. In our routine we conform to the principle of high calorie and high-protein nutrition; this proved to be favorable in the present case.

Swallowing rehabilitation improved the intake of food, permitted high calorie-high protein ingestion, improved the patient's nutritional status and promoted healing of the refractory pressure ulcer.

Case 7: Missed diagnosis of diabetes insipidus A 46-year-old man was transferred to our ward for life support and palliative care after suffering a traumatic head injury, subdural hemorrhage, cardiac arrest and anoxic brain damage. He was in an unaware wakefulness state, received respiratory care through tracheostomy and enteral nutrition through gastrostomy. His medications were phenytoin sodium, levetiracetam and bisacodyl. While hospitalized in neurosurgery, intensive care and subsequently in our ward the diuresis was about 3000 mL/day. Hypernatremia was a constant finding, in the range of 148-156 mEq/L. Spot urine osmolality was 248 mOsm/L. This clinical setting - polyuria associated with hypernatremia subsequent to traumatic brain injury - was suggestive of central diabetes insipidus [31]. The diagnosis was confirmed on normalization of serum sodium, serum osmolality and diuresis under desmopressin treatment. Desmopressin, a synthetic analogue of the antidiuretic hormone, is the drug of choice for the management of central diabetes insipidus. The ease of administration makes it a preferred option for chronic treatment.

Polyuria has been variously defined as urinary output >3000 mL/day, >2500/day, and 50 mL/kg body weight/day. Polyuria-induced dehydration and hypernatremia may lead to organ dysfunction and injury, primarily apparent in the central nervous system and kidneys. Common causes of polyuria in older patients are compulsive water drinking, diabetes mellitus, diuresis following relief of urinary obstruction, diuretic treatment, and all should be considered in the differential diagnosis. Polyuria is also caused by SGLT2 inhibitor treatment for type 2 diabetes mellitus [32]. Diabetes insipidus is a rare cause of chronic polyuria. It is the consequence of decreased arginine-vasopressin (the antidiuretic hormone) secretion or of peripheral resistance to antidiuretic hormone. According to a commonly used algorithm useful in the diagnostic work-up of polyuria, urine osmolality <100 mOsm/L suggests compulsive water drinking, urine osmolality 100-300 is consistent with diabetes insipidus and urine osmolality >1200 mOsm/L is caused by diuretic medication or glycosuria.

Central diabetes insipidus is the result of absent or diminished antidiuretic hormone secretion; administration antidiuretic hormone (the analogue desmopressin) will quickly correct both polyuria and hypernatremia. By this, the diagnosis of central diabetes insipidus is established. Nephrogenic diabetes insipidus shares clinical features with central diabetes insipidus but is resistant to the effect of desmopressin. A variety of disorders may injury the renal tubules making them resistant to antidiuretic hormone. Such are urinary obstruction, infection, severe hypokalemia, severe hypercalcemia and a variety of drugs. Nephrogenic diabetes insipidus is not a rare condition, in distinction from central diabetes insipidus. Treatment of nephrogenic diabetes insipidus should be is tailored to the underlying disorder. The patients should be allowed free access to oral hydration; those incapacitated should receive enteral or parenteral fluid replacement matching the urine output [33].

Acute head trauma can provoke dysfunction of the hypothalamic neurons inducing diabetes insipidus. The disorder becomes apparent in the first days after the trauma and is transient in most patients. In a minority of cases, post-traumatic diabetes insipidus becomes permanent. In the differential diagnosis the main consideration is compulsive water drinking. The diagnosis in our patient was suggested by the clinical setting - polyuria associated with hypernatremia after traumatic brain injury [31] - and was confirmed by normalization of the serum sodium and diuresis under desmopressin treatment. Awareness of diabetes insipidus, a treatable disorder, may be important though rarely met in geriatric care.

Case 8: Thyroxine pseudomalabsorption A 72-year old woman was admitted for treatment of venous ulcers. Her medical background included arterial hypertension, chronic atrial fibrillation, mild chronic renal failure, morbid obesity and hypothyroidism. Her regular medications were furosemide, propafenone, diltiazem and levothyroxine. She was alert and cognitively competent and her vital signs were within the normal range. Unexpected among the routine laboratory tests were high plasma TSH and low FT3 values, contrasting with previous appropriate response to levothyroxine treatment (Table 1).

Date	17/2	25/6	21/7	10/8	11/8
TSH (0.5-4.8 mlu/L)	11.3	7.6	95.6	141	
FT3 (3.5-6.5 pmol/L)	2.3	2.2	1.96	1.65	
T4 (10.3-19 pmol/L)	12.4	15.8	10.1	8.7	
L- thyroxine dose (mcg)	100	100	250	250	250

Table 1: Thyroid function assays under replacement therapy with levothyroxine.

There was a discrepancy between laboratory results and the absence of clinical symptoms of hypothyroidism, such as fatigue, poor concentration, weight gain and constipation. The acute worsening of the thyroid function assays shortly after the patient's admission in the absence of hypothyroid symptoms may be due to laboratory error [34], levothyroxine malabsorption or "Pseudomalabsorption" [35]. Patients should undergo a diagnostic work-up for levothyroxine malabsorption when the TSH levels are persistently high while the patient is receiving daily levothyroxine 2 μg/kg or more. In dubious situations, thyroxine absorption testing is indicated with use of high-dose levothyroxine. But the work-up begins with review of the patient's medications since drugs may interfere with intestinal absorption of levothyroxine. Concomitant administration of levothyroxine with oral iron preparations, calcium, proton pump inhibitors and ciprofloxacin may affect the absorption of levothyroxine. Other drugs may affect the transport and metabolism of levothyroxine; such effects are produced by phenytoin, carbamazepine, estrogens and rifampin. This patient was not receiving any of the listed medications. On reviewing the drug prescription, it became apparent that the patient received levothyroxine just before breakfast (Table 2).

Date	17/2	25/6	21/7	10/8
TSH (0.5-4.8 mlu/L)	11.3	7.6	95.6	141
FT3 (3.5-6.5 pmol/L)	2.3	2.2	1.96	1.65
T4 (10.3-19 pmol/L)	12.4	15.8	10.1	8.7
L- thyroxine dose (mcg)	100	100	250	250
Time of day (a.m)	?	6	8	8

Table 2: Thyroid function assays referred to the time of the day when levothyroxine was administered.

Food may interfere with levothyroxine's absorption; it is mandatory that the drug is administered 1-2 hours before the meals. After advancing the time of levothyroxine administration to 6 a.m., i.e. two hours before breakfast, the response was favourable (Table 3).

Date	10/8	15/8	24/8		24.3.2015
TSH (0.5-4.8 mlu/L)	141	73.6	21.7		10
FT3 (3.5-6.5 pmol/L)	1.65		3.38		
T4 (10.3-19 pmol/L)	8.7		16		21.8
L- thyroxine dose (mcg)	250	250	250	200	150
Time of day (a.m)	8	6	6	6	6

Table 3: Pseudomalabsorption of levothyroxine corrected.

The message is evident: interference of levothyroxine absorption by food should be avoided by taking the hormone 1-2 hours before the meals.

Case 9: Preseptal cellulitis A 58-year-old man, in an unaware wakefulness state following out of hospital resuscitation, was nursed in our institution during the last 7 years. On February 2014 the patient's left eyelids and adjacent skin appeared inflamed and swollen (Figure 4). The temperature was normal and the patient's general condition appeared not to be affected. We referred the

patient for ophthalmologic consultation. He was diagnosed with preseptal cellulitis and advised to be treated with amoxicillin-clavulanate. Within two days the erythema and swelling remitted. Antibiotics were continued for another 5 days. On February 2019 there was recurrence of the disorder on the same side (Figure 5). With the lesson learned the patient was treated in loco. He made an uneventful recovery.

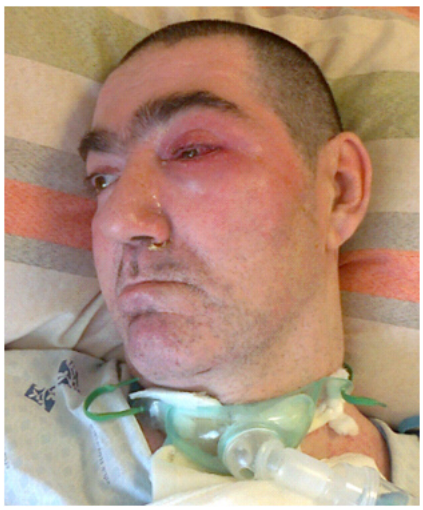

Figure 4: Left eye preseptal cellulitis, 2014.

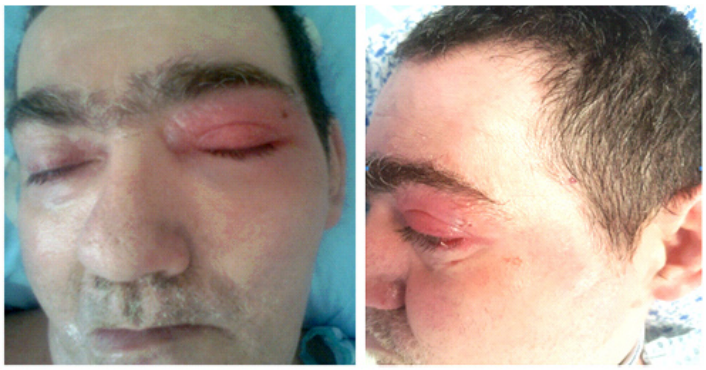

Figure 5: Left eye preseptal cellulitis recurrence, 2019.

Preseptal cellulitis (sometimes called periorbital cellulitis) is an infection of the eyelid and surrounding tissue, not involving the orbit or other ocular structures. It is caused by extension of an extraocular infection or infection through a superficial breakdown of the skin. Serious complications are very rare. Preseptal cellulitis usually responds quickly to systemic antibiotics: clindamycin or TMP-SMX plus one of the following amoxicillin or amoxicillin-clavulanic acid. Topical antibiotics have no role in the treatment of this infection [36]. Vaguely resembling preseptal cellulitis, orbital cellulitis is an infection involving the contents of the orbit (adipose tissue and ocular muscles). Orbital cellulitis is caused by extension to the orbit of an adjacent rhinosinusitis, infection of the teeth, middle ear or face, dacryocystitis, or an infected mucocele eroding into the orbit. Orbital trauma and ophthalmic surgery can also complicate with orbital cellulitis. Orbital cellulitis causes pain on eye movements, presence of proptosis, ophthalmoplegia and diplopia. While preseptal cellulitis is generally a mild condition that rarely leads to serious complications, orbital cellulitis may cause septic optic neuritis, intracranial spread, cavernous sinus thrombosis, and cause loss of vision and even loss of life [37]. It is rare for untreated preseptal cellulitis to extend into the orbit. In case of doubt, computed tomography of the orbits and sinuses may distinguish preseptal from orbital cellulitis.

Preseptal cellulitis typically responds rapidly and completely to appropriate antibiotics. Orbital cellulitis necessitates urgent referral to the ophthalmic surgeon.

Case 10: Priapism due to penile metastases A 66-year-old man was admitted for palliative hospice care. Five years previously he underwent partial resection of the colon for rectal adenocarcinoma. Pulmonary and retroperitoneal metastases responded initially to chemotherapy. Lately the disease became refractory to treatment. The patient's medications included high dose oral morphine, metoclopramide, gabapentin, zopiclone, amitriptyline and tamsulosin. There was need for permanent bladder catheterization. At the time of admission to our ward the patient was cachectic. Numerous subcutaneous nodules were palpable in the abdominal wall. The penis was stiff in partial erection (Figure 6).

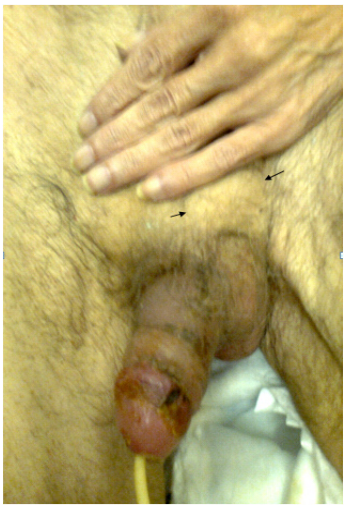

Figure 6: Partially erected penis. One among several adjacent enlarged lymph nodes is visible in the picture under the patient's emaciated hand.

Malignant priapism was diagnosed. A review of the literature in 2016 acknowledged 512 case reports [38]. The primary tumor sites were the bladder, prostate and rectum. According to another review [39], the median survival time after diagnosis of penile metastasis was 10 months (range 6-18 months). Priapism caused by metastases from non-urologic tumors (the case in the present patient) had a worse prognosis. Nonischemic priapism portends no loss of tissue. The glans penis is usually not engorged.

Given the dismal prognosis, palliative noninvasive treatment is advisable. The urology consultant diagnosed in this patient priapism by lymph stasis due to neoplastic lymph nodes invasion. Decompression with elastic bandages was an effective palliation, reducing penile pain and tumefaction over the patient's remaining two months of life.

Discussion

Ten case histories illustrate the complexity of morbidities not infrequent in patients with life-limiting conditions. Patients with any serious illness deserve symptomatic management but also supportive care. Effective collaboration between disciplines improves patient outcomes, is cost effective, and has the broad support of clinical research and treatment guidelines [40,41]. In our experience, collaboration between the internist and oncologist was much rewarding. Consultation with the palliative medicine specialist was implemented occasionally.

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