Pancreatite Aguda Associada a Hipercalcemia como Forma de Apresentação de Hiperparatiroidismo Primário

Acute Pancreatitis Associated with Hypercalcemia as the Initial Presentation of Primary Hyperparathyroidism

Ana Órfão[1], Ana Carolina Monteiro[1], Garcieth Gomes[1], João Pedro Santos[2], Miguel Monteiro[1], Clara Matos[1]

Resumo:

A hipercalcemia secundária ao hiperparatiroidismo primário é uma causa rara de pancreatite aguda.

Apresentamos o caso de uma mulher de 81 anos que foi internada por pancreatite aguda, na ausência dos fatores de risco mais comuns. Como o cálcio total estava ligeiramente aumentado, sendo esperada hipocalcémia na pancreatite aguda, foi colocada a hipótese de hiperparatiroidismo primário. O fósforo sérico baixo e a paratormona elevada também foram consistentes com esta suspeita, tendo o diagnóstico sido confirmado pela cintigrafia das paratiróides, que mostrou tecido paratiroideu hiperfuncionante no polo inferior direito da tiróide.

A doente teve alta hospitalar, aguardando realizar ecografia renal e osteodensitometria para avaliação da presença de nefrolitíase e osteoporose, respetivamente, e da indicação para paratiroidectomia.

Este caso destaca a importância da identificação precoce do hiperparatiroidismo primário como possível causa de pancreatite, para iniciar prontamente a intervenção adequada, prevenindo novos episódios de pancreatite e diminuindo a probabilidade de complicações do hiperparatiroidismo primário.

Palavras-chave: Hipercalcémia; Hiperparatiroidismo Primário/complicações; Pancreatite/etiologia.

Abstract:

Hypercalcemia due to primary hyperparathyroidism is a rare cause of acute pancreatitis.

We present the case of an 81-year-old woman, who was admitted for acute pancreatitis, in the absence of the most common risk factors. Since the total calcium was slightly increased, and hypocalcemia is expected in acute pancreatitis, the hypothesis of primary hyperparathyroidism was suspected. Low serum phosphorus and elevated parathyroid hormone were also consistent with primary hyperparathyroidism, and the diagnosis was confirmed with parathyroid scintigraphy showing hyperfunctioning parathyroid tissue in the lower right thyroid pole. The patient was discharged awaiting to perform renal ultrasound and osteodensitometry to assess the presence of nephrolithiasis and osteoporosis, respectively, to evaluate the indication for parathyroidectomy.

This case highlights the importance of early identification of primary hyperparathyroidism as a possible cause of pancreatitis to promptly start the proper intervention, preventing further episodes of pancreatitis and decreasing the likelihood of complications of primary hyperparathyroidism.

Keywords: Hypercalcemia; Hyperparathyroidism, Primary/complications; Pancreatitis/etiology.

Learning points

1. Acute pancreatitis can have various underlying causes, and primary hyperparathyroidism (PHPT) should be considered, especially in patients presenting with hypercalcemia, even when common risk factors like alcohol use and gallstones are absent.
2. Monitoring serum calcium levels is crucial in cases of acute pancreatitis, as hypocalcemia is typically expected. An elevated calcium level can signal underlying conditions such as PHPT
3. Early identification and treatment of PHPT can prevent further episodes of pancreatitis and reduce the risk of complications associated with the disorder.

Introduction

Primary hyperparathyroidism (PHPT) is a metabolic bone disorder characterized by the excessive secretion of parathyroid hormone (PTH) due to the hyperactivity of the parathyroid gland. Postmenopausal women aged over 50 years exhibit an increased likelihood of developing PHPT.[1]

The predominant etiology of PHPT is the presence of parathyroid gland adenomas, accounting for 80% to 85% of the

[1]Serviço de Medicina 3, Unidade Local de Saúde Amadora/Sinta, Amadora, Portugal
[2]Intensive Care Medicine, Unidade Local de Saúde Amadora/Sinta, Amadora, Portugal

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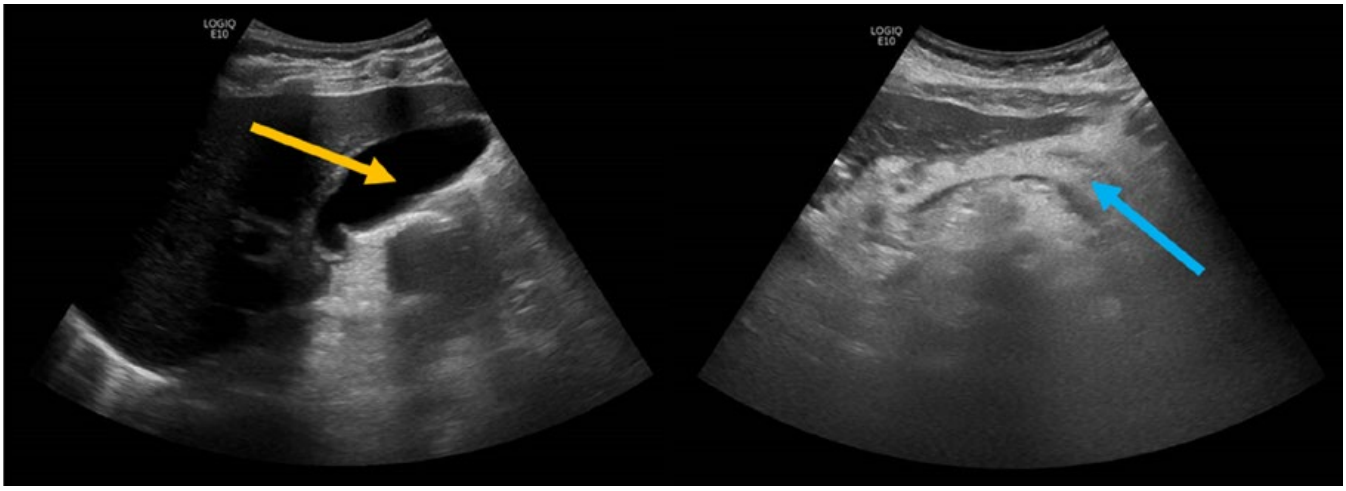

Figure 1: Abdominal ultrasonography excluded cholelithiasis (yellow arrow) and revealed a globular pancreas (blue arrow), with no dilation of the main pancreatic duct in the segments visualized (cephalic portion and body), suggesting acute acalculous pancreatitis.

Assuming acute acalculous pancreatitis, with a BISAP score of 2 (blood urea >25 mg/dL and age >60 years), the patient was admitted for in-hospital treatment in an Intermediate Care Unit and started aggressive intravenous fluid therapy, analgesics and antiemetics. After pain and vomiting control, oral nutrition was started, about 24 hours after admission, with a low-fiber and low-fat diet. Two days after admission, the RANSON score was 3 (age >55 years, glucose >200 mg/dL, and hematocrit drop >10% from admission), inflammatory parameters were increasing, and the patient was febrile. Abdominal and pelvic computed tomography (CT) with intravenous (IV) contrast (Fig. 2) excluded cholelithiasis, as well as complications of pancreatitis, such as necrosis.

No dilation of the main pancreatic duct was observed. Additionally, it evidenced mild bilateral pleural effusion in both lung bases, as well as moderate ascites, an enlargement of the cephalic portion of the pancreas, and moderate densification of peripancreatic fat.

cases. Less common causes include parathyroid hyperplasia, carcinoma, multiple endocrine neoplasia type 1 and 2A, as well as parathyroid cysts.[2]

The pancreas can be affected by hypercalcemia secondary to PHPT, leading to acute, subacute, or chronic pancreatitis.[3] The recognition of PHPT is frequently missed or delayed since the symptoms are non-specific, and serum calcium is not frequently measured in cases of acute pancreatitis.[1]

Case Report

We present the case of an 81-year-old woman, with a previous history of arterial hypertension (medicated with azilsartan 80 mg once daily, lercanidipine 20 mg once daily, and bisoprolol 5 mg once daily), type 2 diabetes *mellitus* with stage 3 chronic kidney disease (medicated with dapagliflozin 10 mg once daily, and insulin glargine), and atrial fibrillation (anticoagulated with rivaroxaban 15 mg).

The patient was admitted to the emergency department with complaints of incoercible vomiting lasting 12 hours, associated with epigastric pain radiating to the back.

The patient had no history of alcohol intake, medication or drug abuse, and no personal or family history of hyperlipidemia or pancreatitis. She also denied any new medications that could possibly cause acute pancreatitis, as well as any history of nephrolithiasis, neuropsychiatric symptoms or muscle weakness.

On admission, the patient was conscious, with a blood pressure of 121/76 mmHg, pulse rate of 89 beats per minute, and apyretic. She had epigastric tenderness, without rigidity or guarding, ad the remaining physical examination was normal.

Blood investigation (Table 1) revealed leukocytosis with neutrophilia, normal C-reactive protein (CRP), a significantly increased amylase, increased blood urea with creatinine similar to the basal level, and normal liver tests.

Abdominal ultrasonography (Fig. 1) excluded cholelithiasis and revealed a globular pancreas, with no dilation of the main pancreatic duct, suggesting acute acalculous pancreatitis. In addition, a thin film of peripancreatic and subhepatic pure fluid was identified, as well as slight parietal edema in the topography of the duodenal arch, in contiguity with the inflammatory process.

Although initially attributed to the systemic inflammatory phase in acute pancreatitis, in light of persistent fever at day 5 of illness, associated with increasing CRP (31.6 mg/dL) and procalcitonin (0.38 ng/mL), the diagnosis of intra-abdominal infection was presumed, and the patient was treated empirically with piperacillin-tazobactam for seven days. Blood cultures were negative. By the end of treatment, the patient showed improvement in clinical and biochemical parameters (resolution of fever and decrease of CRP), allowing the reduction of intravenous fluids, with concomitant improvement of pleural effusion.

Following the exclusion of the two most common causes of acute pancreatitis (alcohol and gallstones), further investigation was made to look for the etiology of acute pancreatitis,

Table 1: Laboratory investigation.

Parameter (unit)	Admission	48 hours after admission	Complementary investigation	Normal Range
Hemoglobin (g/dL)	13.0	10.2	-	12.0 - 15.0
Hematocrit (%)	39.6	32.0	-	36.0 - 46.0
Leukocytes (x 10^9/L)	15.9	16.3	-	4.0 - 10.0
Platelets (x 10^9/L)	249	163	-	150 - 410
Erythrocyte sedimentation rate (mm/h)	-	104	-	< 20
Total calcium (mg/dL)	10.4	10.3	-	8.8 - 10.2
Albumin (g/dL)	3.59	2.77	-	3.97 - 4.94
Corrected calcium (mg/dL)	10.7	11.3	-	8.8 - 10.2
Inorganic phosphorus (mg/dL)	1.9	2.1	-	2.5 - 4.5
AST (U/L)	25	-	-	< 32
ALT (U/L)	30	-	-	< 33
ALP (U/L)	87.28	-	-	35.00 - 105.00
GGT (UI/L)	15	-	-	< 40
LDH (U/L)	174	-	-	135 - 214
Total bilirubin (mg/dL)	0.65	-	-	≤ 1.20
Creatinine (mg/dL)	1.67	0.90	-	0.50 - 0.90
Urea (mg/dL)	137.5	41.5	-	< 50.0
Glucose (mg/dL)	185	-	-	74 - 109
Amylase (U/L)	>75000	-	-	28.0 - 100.0
Triglycerides (mg/dL)	141	-	-	< 150
CRP (mg/dL)	0.57	23.44	-	< 0.50
TSH (mUI/L)	-	-	1.48	0.270 - 4.200
iPTH (pg/mL)	-	-	140.0	15.0 - 65.0
25-hydroxy vitamin D (ng/mL)	-	-	10.60	Severe deficit <10; Moderate deficit 10-29; Recommended values 30-100; Toxic values >150
24-hour urine calcium (mg/24h)	-	-	58.80	100.00 - 300.00
Urinary creatinine, occasional measurement (mg/dL)	-	-	92	28 - 217
Complement C4 (mg/dL)	-	-	32.1	10.0 - 40.0
Complement C3 (mg/dL)	-	-	133	90 - 180
IgG (mg/dL)	-	-	676.00	700 - 1600
IgG 4 (mg/dL)	-	-	61.70	3.90 - 86.40
IgA (mg/dL)	-	-	145.60	70.00 - 400.00
IgM (mg/dL)	-	-	34.74	40.00 - 230.00
ANA	-	-	Negative	
EBV antibodies				
Anti-VCA IgG	-	-	Positive	
Anti-VCA IgM	-	-	Negative	
Anti-EBNA	-	-	Positive	
CMV antibodies				
Anti-CMV IgG	-	-	Positive	
Anti-CMV IgM	-	-	Negative	
Anti-HIV-1/2 Ab / p24 Ag	-	-	Non-reactive	

alkaline phosphatase: ALP, alanine transaminase: ALT, antibody: Ab, antigen: Ag, antinuclear antibodies: ANA, aspartate transferase: AST, component 3: C3, component 4: C4, cytomegalovirus: CMV, Epstein Barr virus: EBV, human immunodeficiency virus: HIV, gamma-glutamyl transferase: GGT, lactic dehydrogenase: LDH, immunoglobulin A: IgA, immunoglobulin M: IgM, immunoglobulin G: IgG, intact parathyroid hormone: iPTH, thyroid stimulating hormone: TSH.

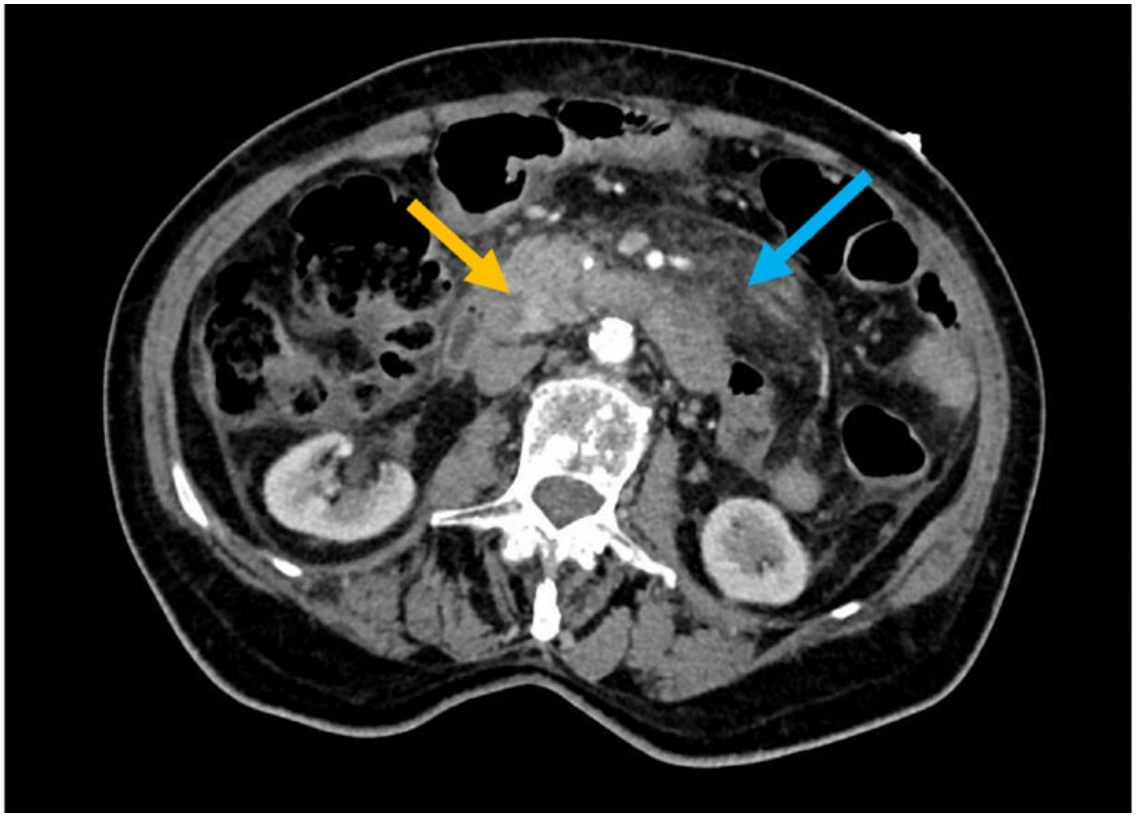

Figure 2: Abdominal and pelvic CT with contrast showed a pancreas with an enlarged cephalic portion (yellow arrow) with irregular contrast distribution and moderate densification of peripancreatic fat (blue arrow) and thickening of the renal fascia bilaterally.

revealing a normal lipid profile, and no clinical or analytical evidence of autoimmune disease. Since the total calcium was slightly increased, and hypocalcemia is expected during an acute episode of pancreatitis, the hypothesis of PHPT was made. The other suggestive parameters were low serum phosphorus, elevated intact PTH and low 25-hydroxy vitamin D. Urinary calcium was low, but it could be secondary to vitamin D deficiency. Parathyroid scintigraphy (Fig. 3) showed, in the late images, a persistent focus of radiopharmaceutical uptake in the projection of the lower pole of the right thyroid lobe, with a nearly homogeneous washout of the radiopharmaceutical in the remaining parenchyma. This finding was suggestive of hyperfunctioning parathyroid tissue in the lower right thyroid pole, confirming the diagnosis of PHPT.

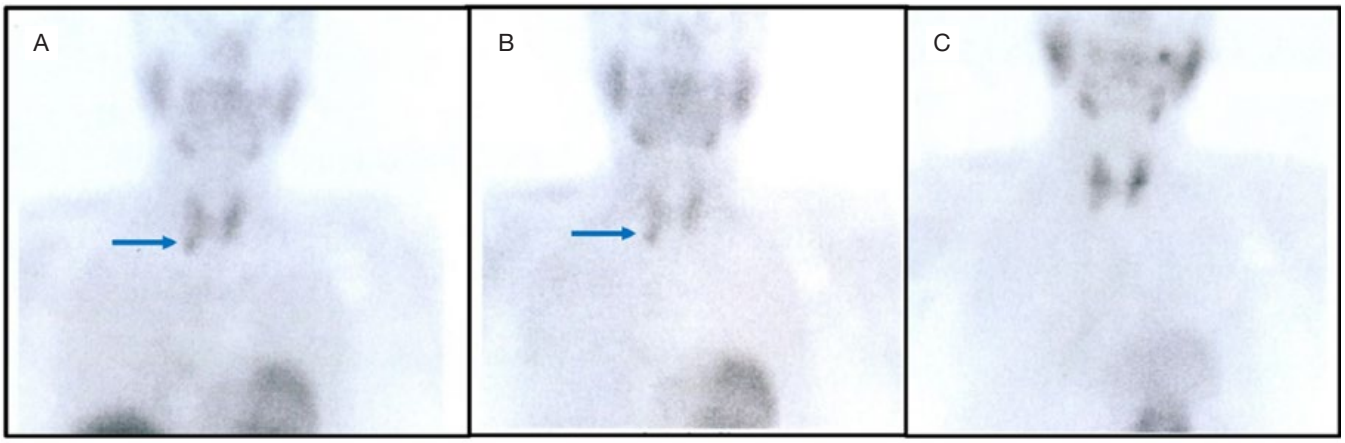

Figure 3: Radionuclide parathyroid imaging. **(A)** The early 10-minute [99mTc]Tc-Tetrofosmin image shows good tracer uptake in the thyroid gland with relatively focal and increased uptake in the right lower pole (arrow). **(B)** The late 2-hour image shows focal retention of tracer in the region of the right lower pole of the thyroid gland, which is suspicious of the right lower pole parathyroid adenoma (arrow). **(C)** Thyroid scan appearances are compatible with thyroid nodules on the middle third of the left thyroid lobe, without nodular changes in the right lower pole.

After the resolution of acute pancreatitis, mild hypercalcemia and hypophosphatemia persisted.

The patient was later discharged, medicated with vitamin D supplements, advised for adequate hydration, and referred to an Endocrinology consultation, awaiting to complement the PHPT study with renal ultrasound and osteodensitometry to assess the presence of nephrolithiasis and osteoporosis, respectively, to evaluate the indication for surgical intervention with parathyroidectomy.

Discussion

The incidence of pancreatitis associated with PHPT has been seen to vary between 1.5% and 15.3% among patients aged 20 to 70 years,[4] (with no data available for patients beyond this age) and the most important reason for these different rates is the heterogeneity of the PHPT severity.[3]

There are several physiopathological hypotheses proposed to elucidate the underlying mechanisms between pancreatitis and PHPT. To begin with, hypercalcemia is associated with elevated levels of calcium in the pancreatic juice, enhancing the conversion of trypsinogen to trypsin, which is an active protease responsible for the pathological aggression of the pancreatic parenchyma and ducts.[1,3-5] Additionally, individuals with hypercalcemia exhibit reduced pancreatic secretion levels, but the enzyme activity remains unaffected, leading to the development of protein plugs inside the pancreatic ducts, which might culminate in the obstruction of the ducts, leading to self-digestion of the pancreas.[1,3,4] Calcifications may also contribute to the occlusion of the pancreatic duct.[1,3-5] It is also believed that PTH contributes to the development of pancreatitis by the inhibition of pancreatic vascularisation or the induction of microthrombi formation, resulting in necrosis of the pancreatic parenchyma.[4] Finally, certain genetic mutations, such as the cystic fibrosis transmembrane conductance regulator (CFTR) mutation, when combined with hypercalcemia, significantly elevate the likelihood of pancreatitis in individuals with PHPT.[5]

The diagnosis of PHPT is typically made following the occurrence of multiple episodes of pancreatitis,[4] through the identification of an increased PTH level in a patient presenting with asymptomatic hypercalcemia.[1] Fortunately, in this case, the diagnosis was made in the first episode of acute pancreatitis.

The serum calcium level typically exhibits a decrease during episodes of acute pancreatitis.[1,3] Therefore, elevated serum calcium levels, together with hypercalciuria and hypophosphatemia, should prompt further investigation into underlying secondary causes, namely endocrine or neoplastic etiologies, hence reducing diagnostic and treatment delays.[1] In the present case, hypercalcemia strongly suggested the possibility of PHPT.

The initial management of acute pancreatitis resulting from PHPT and hypercalcemia is similar to every other type of acute pancreatitis, which includes aggressive fluid replacement (4-6 L can be administered in the first 24 hours). In this particular scenario, the use of a normal saline solution may be deemed more favourable due to the presence of calcium in the lactated ringer's solution.[4] After reaching normovolemia, the administration of either oral or intravenous fluids is continued to maintain adequate urine output.

Secondly, enteral nutrition is believed to preserve the integrity of the gastrointestinal tract, hence reducing the translocation of bacteria and subsequent activation of an inflammatory response. It is suggested that the early outset of enteral nutrition, within 48 hours of initial presentation, can enhance survival rates and reduce the probability of surgical intervention.[4]

The administration of prophylactic antibiotic therapy is generally not recommended in cases of acute pancreatitis. It should only be considered if there is evidence of infection in the necrotic areas and after drainage of the collections if present.[4]

Due to the elevated rates of morbidity and mortality associated with acute pancreatitis, it is imperative to prioritize the treatment of pancreatitis, instead of PHPT. Following the resolution of pancreatitis, parathyroidectomy should be kept in mind, particularly in the presence of recurrent nephrolithiasis, clinically evident bone disease or severe hypercalcemia.[1]

Surgery remains the sole therapeutic option for managing symptomatic PHPT and achieving a lasting cure, by normalizing serum calcium and PTH levels, and reducing the probability of pancreatitis recurrence.[3]

Conclusion

Hypercalcemia due to PHPT is a rare cause of acute pancreatitis, possibly due to underdiagnosis given the non-specific symptoms and lack of measurement of serum calcium during episodes of acute pancreatitis. Thus, in the absence of common risk factors, this hypothesis should be considered and promptly investigated, particularly in the setting of recurrent pancreatitis. Although it does not influence the clinical course of acute pancreatitis, the diagnosis of underlying PHPT allows for a targeted treatment of the cause of pancreatitis, thus preventing future recurrence.

The present case highlights the importance of an extensive investigation of the etiology of acute pancreatitis, after ruling out the most common causes, leading to an early diagnosis of PHPT. ■

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AO, AM – Pesquisa bibliográfica e redação do artigo

GG, JS, MM – Revisão do artigo

CM – Revisão final do artigo

Todos os autores aprovaram a versão final a ser publicada

Contributorship Statement

AO, AM - Literature research and writing the article

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Correspondence / Correspondência:

Ana Orfão - anaorfao_3@hotmail.com

Serviço de Medicina 3, Unidade Local de Saúde Amadora/Sinta, Amadora, Portugal

IC19 276, 2720-276 - Amadora

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