ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Pork-cat syndrome as cause of anaphylactic reaction to well-cooked meat

Síndrome gato-porco como causa de reação anafilática à carne cozida

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ABSTRACT

Pork-cat syndrome is a rare clinical syndrome that can cause life-threatening reactions. Occuring in patients allergic to cat dander, it involves cross-reactivity between cat and pig serum albumin. Cat allergy usually precedes food allergies, suggesting primary sensitization to cat serum albumin. Since these proteins are thermolabile, the reaction tends to be more severe in undercooked meat. A 27-year-old woman with persistent moderate-to-severe rhinoconjunctivitis since childhood reported 2 immediate mucocutaneous reactions after eating small amounts of pork. Skin prick tests with commercial extracts showed sensitization to pork, and prick-to-prick tests confirmed sensitization to raw pork and raw beef. Specific IgE was positive for pork, and ISAC microarray also showed sensitization to Fel d 2. SDS-PAGE and IgE immunoblotting assays were performed with raw and cooked pork extract and detected in a 60 kDa band. In the immunoblotting-inhibition assays, cat serum albumin completely inhibited IgE binding to pork extract. The patient underwent 2 oral food challenges with well-cooked pork and beef, both causing an anaphylactic reaction. The patient's history and in-vivo and in-vitro tests led to a diagnosis of pork-cat syndrome with clinical cross-reactivity to another mammalian serum albumin. This case should stimulate oral food challenges with other well-cooked mammalian meats in patients with this syndrome to establish a tolerance threshold and avoid possible unexpected anaphylactic reactions.

Keywords: Cross-reactivity, serum albumin, severity, pork-cat syndrome.

RESUMO

A síndrome gato-porco é rara e ocorre em doentes alérgicos ao pêlo de gato, envolvendo reatividade cruzada entre as albuminas séricas (AS) de gato e de porco. Normalmente, a doença respiratória a pêlo de gato precede a alergia alimentar, sugerindo uma sensibilização primária à albumina sérica de gato. Uma vez que estas proteínas são termolábeis, as reações tendem a ser mais graves com carnes menos cozidas. Mulher de 27 anos com rinoconjuntivite persistente moderada a grave desde a infância que refere duas reações imediatas mucocutâneas após ingestão de pequenas quantidades de carne de porco. Os testes cutâneos por picada com extratos comerciais mostraram sensibilização à carne de porco e os testes *prick-to-prick* confirmaram sensibilização à carne de porco e de vaca cruas. A IgE específica (sIgE) foi positiva para carne de porco, e o ensaio ISAC mostrou sensibilização a Fel d 2. Foram realizados ensaios de *immunoblotting* SDS-PAGE IgE com extratos de carne de porco crua e cozidas que detectaram uma banda de 60 kDA. Nos ensaios de inibição por *immunoblotting* a albumina sérica de gato produziu uma inibição total da ligação da IgE ao extrato de carne de porco. A doente realizou duas provas de provocação oral com carne de porco e de vaca cozidas, ambas positivas com desenvolvimento de reação anafilática. A história clínica, os testes *in-vivo* e *in-vitro* levaram ao diagnóstico de síndrome gato-porco com reatividade cruzada clínica a outras albuminas séricas de mamíferos. A síndrome gato-porco é rara e pode causar reações fatais. Este caso frisa a importância da realização de provas de provocação oral com outras carnes de mamíferos bem cozidas em doentes com esta síndrome, de forma a estabelecer um limiar de tolerância e evitar possíveis reações anafiláticas inesperadas.

Descritores: Reatividade cruzada, albumina sérica, severidade, síndrome gato-porco.

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Background

Food allergies are increasing in prevalence and severity. Up to 60%[1] of the reactions in older children, adolescents, and adults are related to cross-reactivity between aeroallergens and food allergens. Primary food allergy with sensitization to food allergens can also occur, mainly in the gastrointestinal tract.[1,2]

Cross-reactivity is an immune-mediated reaction in which IgE antibodies that are produced to recognize a specific allergen react to a homologous one, inducing an immune response. This mainly occurs with closely related allergen molecules of phylogenetically close species or in more distant species between well-preserved molecules belonging to the same protein family and having similar functions.

Pork-cat syndrome, first described by Drouet et al. in 1994,[3] is a primary IgE-mediated respiratory allergy to cat dander followed by a food allergy to pork. The prevalence of this syndrome is unknown, and there are few published reports about it.[4-7] It results from an IgE antibody against a protein with a molecular weight of approximately 67 kDa, later identified as cat albumin Fel d 2 (minor cat allergen).[8,9] It has high homology (79.1% AA-sequence identity) with pork albumin, and the cross-reactivity between them is responsible for the symptoms. The severity of the reaction may vary from slight (mucocutaneous symptoms) to anaphylaxis. Since serum albumins are generally heat labile, the probability that well-cooked meat will cause severe reactions should be lower.[1]

Case presentation

We describe the case of a 27-year-old woman born in Mozambique who has lived in Lisbon since 20 years of age. While living in Africa she ate neither pork (for religious reasons) nor beef (due to dislike). Since moving to Portugal, she has occasionally eaten small quantities of pork. In childhood, she always had outdoor cats and dogs, but in Lisbon she got an indoor dog and cat at 22 and 24 years of age, respectively. Since adolescence she has had a history of persistent moderate-to-severe rhinoconjunctivitis that worsened indoors and at night, but noticed that it had been worsening since she was 24 years of age. She denied symptoms suggestive of bronchial hyperactivity. She reported 2 mucocutaneous reactions about 30 min after ingesting small amounts of pork. The first occurred when she was 21 years of age, with labial edema and urticaria after eating a meal with pork, after which she began to avoid it. The second episode occurred some years later, with urticaria and angioedema after accidental intake of a pork croquette (thinking it was chicken). She sometimes handled pork when helping her sister cook meals, which resulted in contact angioedema but no other symptoms. She also reported oropharyngeal pruritus related to beef, so she began avoiding that as well. She had no symptoms suggestive of cow milk allergy.

Skin prick tests with commercial extracts revealed sensitization to *Blomia tropicalis* (8 mm), *Acarus siro* (7 mm), olive pollen (13 mm), grass pollen (7 mm), cat dander (9 mm), dog dander (7 mm), and pork (5 mm). Prick-to-prick tests showed sensitization to raw pork (11 mm) and raw beef (5 mm) but were negative for well-cooked pork and beef. She also developed pruritus after 3 min and an erythematous papule 5 min after 5-minute contact with raw pork on the skin, which are compatible with immediate reaction. Contact testing with cooked pork and raw and cooked beef was negative. These results are shown in Figure 1. Serum total immunoglobulin E (IgE) was elevated (401.0 kU/L). Specific IgE was positive for cat dander (38.9 kUA/L), pork (3.47 kUA/L), *Blomia tropicalis* (2.33 kUA/L), *Acarus siro* (2.45 kUA/L), olive pollen (4.37 kUA/L), and Dactylis glomerata pollen (6.72 kUA/L). ImmunoCAP ISAC microarray (Thermo Fisher Scientific, Waltham, MA, USA) showed very high sensitization to Fel d 4; high-to-moderate sensitization to Fel d 1, Fel d 2, Can f 1, Can f 3, Phl p 1, and Phl p 4; and low sensitization to Equ c 1, Equ c 3, Cyn d 1, Mus m 1, and Ole e 1.

Extracts from raw and cooked pork were prepared by delipidation with acetone, homogenization in phosphate buffered saline (20% w/v) (50 mM phosphate buffer, 100 mM NaCl, pH 7.5) with magnetic stirring, centrifugation, dialysis of the supernatants against distilled water, and lyophilization. Sodium dodecyl sulphate- polyacrylamide gel electrophoresis (SDS-PAGE)/IgE immunoblotting assays were performed with raw and cooked pork extract, and a 60 kDa band was detected in both samples. In the immunoblotting-inhibition assays, cat albumin completely inhibited IgE binding to pork extract (Figure 2). We also performed an inhibition assay with other mammalian meat (lamb), which showed cross-reactivity with pork and cat albumin (results not shown).

The patient underwent 2 oral food challenges with cooked pork and beef, both of which were positive and with an anaphylactic reaction. In the first challenge, she developed urticaria, angioedema,

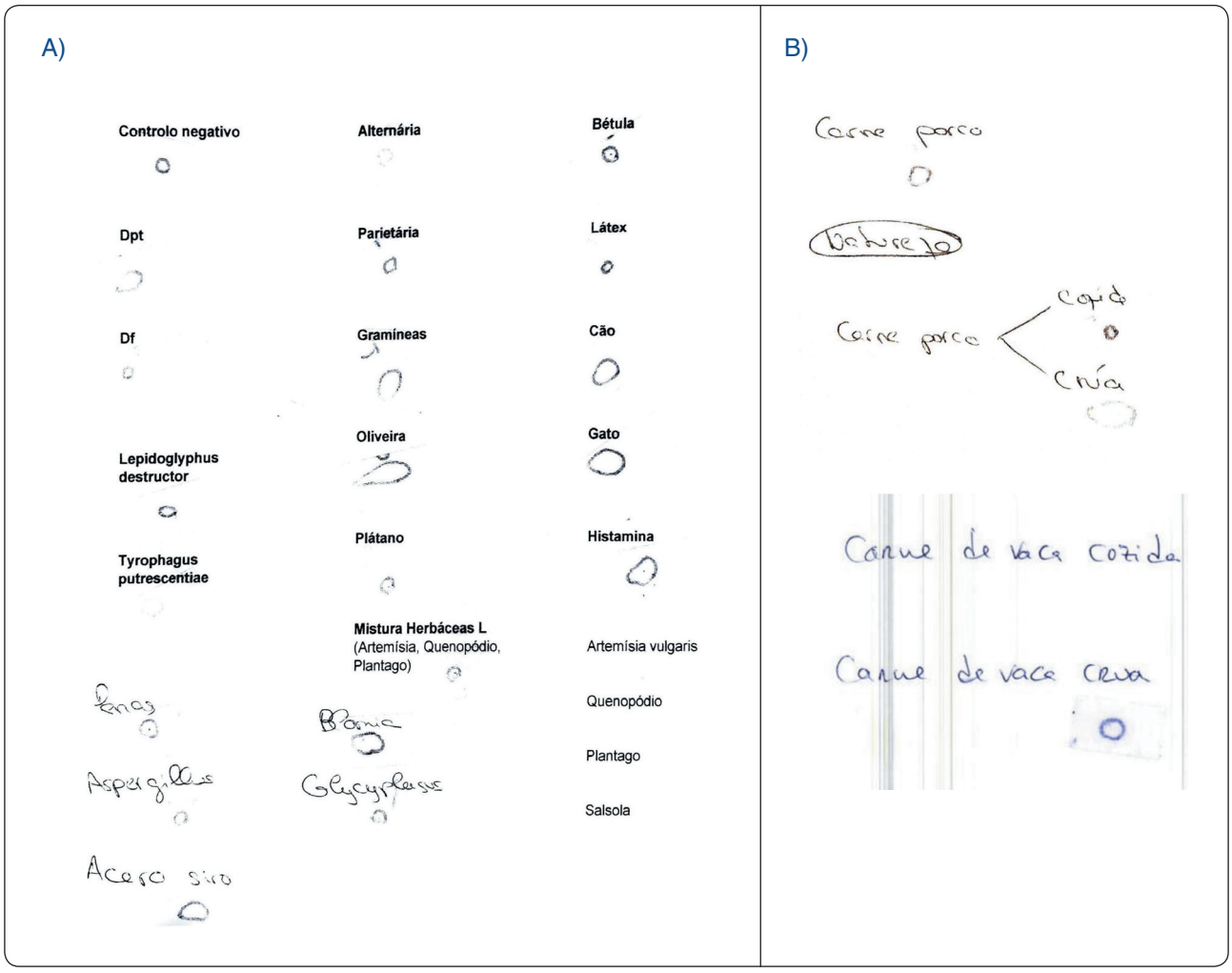

Figure 1
A) Skin prick tests showing sensitization to mites, pollens, and pork.
B) Prick-to-prick tests showing sensitization to raw pork and beef.

nasal blockage, serous discharge, and eye and nasal pruritus 15 min after ingesting 2 g of well-cooked pork, followed by dysphonia, dry cough, and uvula edema. She was treated with 2 doses of 0.5 cc epinephrine IM, anti-histamine, and corticosteroid, with clinical improvement in 30 min.

In the second challenge, she developed cough, dysphonia, lightheadedness, and throat tightness 10 min after ingesting 8 g of well-cooked beef, with immediate improvement after 0.5 cc of epinephrine IM.

The patient's history and *in vivo* and *in vitro* test results led to a diagnosis of pork-cat syndrome with clinical cross-reactivity to another mammalian meat. An epinephrine auto-injector was prescribed, and the patient was advised to maintain a diet free of mammalian meat. Medical treatment led to slight improvement in rhinoconjunctivitis, but the patient reported exacerbation in closed spaces (home and office). Contrary to our advice, she made no environmental changes to reduce exposure to aeroallergens. Since then, we have heard nothing further from her.

Discussion and conclusions

Pork-cat syndrome is rare and can go unnoticed if not properly assessed. In this case, the patient had a primary sensitization to cat dander, with an evident respiratory allergy that worsened with exposure to

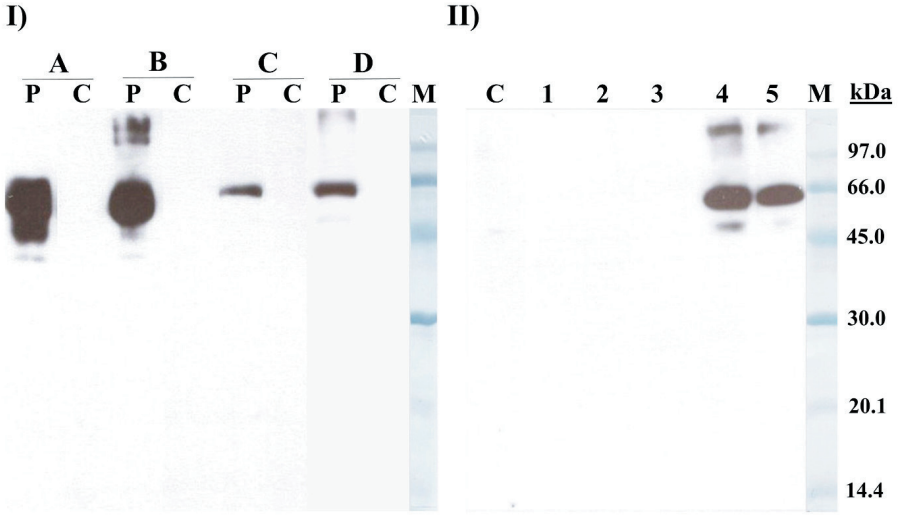

Figure 2

I) SDS-PAGE/Immunoblotting. A) Cat dander extract, B) Cat serum albumin, C) Raw pork extract, D) Cooked pork extract. Lane P: Patient serum, Lane C: Control serum (pool of sera from non-atopic individuals), Lane M: Molecular mass standard.

II) SDS-PAGE/Immunoblotting-inhibition. Solid phase: Pork extract. Lane C: Control serum (pool of sera from non-atopic individuals), Lanes 1-5: Patient serum pre-incubated with pork extract (lane 1), Cat dander extract (lane 2), Cat albumin (lane 3), Chicken ovalbumin (lane 4), and Sunflower pollen extract (lane 5), Lane M: Molecular mass standard.

high levels of the allergen (when she owned an indoor cat). She was not exposed to pork during childhood, but when she moved to Lisbon, she began to have meals that contained it. We cannot assess the role of its late introduction in food allergy development. As reported by other authors,[10-13] she also had symptoms with beef, most likely due to cross-reactivity between serum albumins.

The laboratory workup proved sensitization to cat dander and pork: ISAC assay showed sensitization to Fel d 2 (cat albumin), SDS-PAGE/IgE immunoblotting detected a 60 kDa band (as shown in Hilger et al.[12]), and the immunoblotting-inhibition assays showed cross-reactivity between cat and pork albumin.

The pork food challenge established the clinical relevance of sensitization. The anaphylactic reaction to well-cooked pork was not expected because serum albumin is heat labile, losing its IgE reactivity after exposure to high temperatures. The results of both food challenges highlight why they are considered the gold standard for diagnosing food allergies, as well as their important prognostic value, determining the tolerance threshold and risk of severe reaction.

Besides sensitization to cat dander and cat serum albumin, ISAC also showed sensitization to dog, horse, and mouse, which is explained by the cross-reactivity between serum albumin of different mammals.

Regarding aeroallergens, the patient was sensitized to *Blomia tropicalis* and *Acarus siro*, two uncommon mites in Lisbon, according to the 2011 mite map of Portugal[13]. This, plus the fact that the patient worsened when she acquired an indoor cat, suggest that the most probable cause of worsening rhinoconjunctivitis was exposure to cat dander.

Since both respiratory and food allergies are generally caused by Fel d 2 sensitization, we hypothesize specific immunotherapy to cat dander as a possible treatment for our patient. One year of subcutaneous immunotherapy with cat dander extract has led to symptom improvement in adults with rhinoconjunctivitis and asthma.[14] However, Fel d 1 is the only standardized allergen in specific immunotherapy for cat dander, since this is the major cat allergen. The effects of such a therapy could be studied in patients co-sensitized to Fel d 1 and Fel d 2. Furthermore, its efficacy for pork allergy in pork-cat syndrome could also be determined, since there is currently no treatment for this syndrome.

Pork-cat syndrome is a rare clinical syndrome that can cause life-threatening reactions. Molecular analysis is fundamental to document cross-reactivity, but oral food challenges should always be performed to define the tolerance thresholds of each patient. By doing so the clinician can define which patients are at risk of anaphylaxis and develop action plans to avoid the worst clinical manifestations.

This is the third pork-cat syndrome case published to date in Portugal and it involved the most severe clinical symptoms. Our report shows the need for better awareness of this syndrome and its potentially life-threatening consequences.

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