Figure 3 Results of patch testing with 10% pantoprazole in white petrolatum in a patient with exfoliative eryhthroderma. Reading taken at 72 h after patch application.

cases of pantoprazole-induced severe cutaneous reactions of the type Stevens–Johnson syndrome and toxic epidermal necrolysis.[5] Isolated reports of lichenoid eruption, acute interstitial nephritis, neutropenia, and vasculitis attributed to proton pump inhibitors, including pantoprazole, have also been published.[6–10]

To the best of our knowledge, this is the first report of a case of exfoliative erythrodermia induced by pantoprazole that was confirmed by drug patch testing. Although a positive patch test does not constitute an absolute diagnostic criterion for establishing drug responsibility in this particular case, it is interesting to mention that the test was negative in non-allergic control subjects, and was also negative for all other drugs tested in the present patient. Therefore, an irritating reaction to the patch test seemed less likely to be occurring. Even though this diagnostic tool has not been adequately standardised, it is useful for a more precise diagnostic evaluation especially in patients who are receiving multiple medications, as was the case in the present report.

With regard to the management, since in patients with immediate reactions to proton pump inhibitors cross-reactions between omeprazole and pantoprazole but not with lanzoprazole are observed, we recommended the use of lanzoprazole, which has been tolerated by this patient during the short three-month follow up period after its initiation.

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Resolution of IgE-mediated fish allergy

To the Editor,

Fish is a common allergen source, being one of the most frequent causes of IgE-mediated food allergy in children, in many countries. Severe clinical reactions to multiple fish are usual.[1] This is mainly justified by their major allergens, parvalbumins, which are thermo-acid resistant proteins (maintaining its structure when cooked or submitted to a pH as low as 2.75 in the digestive process) and ubiquitous in various fish (although expressed in different levels).[1–3] Fish allergy usually manifests during early childhood and is considered mainly as persistent, likely to be lifelong.[1] Despite this, there has been one report of fish allergy outgrown in adulthood.[4] A pattern of fish allergy in which evolution tends towards tolerance of all fish over the years has also been described.[5] These fish allergic patients are typically young children, who tolerate some fish (Tunidae and Xiphiidae families), despite reacting to other species.[5] However, when several severe clinical reactions to various fish from different taxonomic families have occurred for a long period of time or if the patient is highly sensitised to multiple fish, a complete fish exclusion diet is usually advised for life. In this paper, we present and discuss a case of long-term follow-up successful management of a patient with lasting and severe fish allergy that has resolved.

Table 1 Skin prick test results (commercial extracts)

Fish	Age (years)							
	1	3	4	6	8	12	14	16
Hake	+	+	+	nd	nd	+	+	+
Cod	+	+	+	+	+	+	+	+
Tuna	nd	nd	–	+	–	+	–	–
Sole	nd	nd	nd	+	+	–	–	–
Salmon	nd	nd	+	+	nd	nd	–	–
Sardine	+	+	+	+	+	+	+	+
Monkfish	nd	nd	nd	nd	nd	+	–	–

+, positive skin prick test (i.e. wheal mean diameter ≥3 mm); –, negative skin prick test; nd, not done.

Table 2 Specific IgE determination (Immulite 2000®, kU/L)

Fish	Age (years)		
	12	14	16
Hake	<0.35	<0.35	0.10
Cod	1.56	1.43	0.86
Tuna	<0.35	0.47	0.32
Sole	nd	0.43	0.17
Salmon	nd	2.14	0.99
Sardine	nd	2.31	1.01

nd, not done.

The authors describe the case of an 18-year-old Portuguese male. He has a medical history of eczema since early infancy, allergic rhinitis and asthma since four years of age (controlled with daily nasal and inhaled budesonide). Hake was first introduced into his diet when he was seven months old. Although he had tolerated fish for about three months, without any problems, his mother reported two sudden episodes of difficulty in breathing, stridor, urticaria and vomiting, immediately after hake and mackerel ingestion, when he was 10 and 11 months old, respectively. At the time, skin prick tests (SPT) using commercial extracts yielded positive results to fish (Table 1). Considering this, fish avoidance was advised and a therapeutic action plan, in case of reaction, was explained. After a fish-free diet for two years, without any further allergic episodes, an oral food challenge (OFC) with hake was performed. Following ingestion of 1 mg of cooked fish, perioral urticaria and mild wheezing difficulty in breathing developed. Complete fish avoidance was again recommended. In the following years, the patient was regularly evaluated, maintaining positive SPT to various fish (Table 1). Two accidental exposures occurred, also eliciting facial urticaria and dyspnoea, the last when the child was 11 years of age, after having eaten cereals in a redfish contaminated bowl (having always tolerated the cereals, before and after this allergic reaction). Symptoms have never occurred by direct inhalation or contact with fish. From 12 years of age, serum specific IgE (sIgE) determinations to fish were available at the Department (Table 2). At 14-years-old, he and his family agreed to try to reintroduce fish into the diet. Open OFC to tuna, sole, salmon, hake, and cod were sequentially performed (separated by six months mean time intervals), being all negative. They were performed in a hospital setting, under medical supervision, using gradually increasing doses, given every 20 min, until a cumulative amount of fish similar to that of a normal meal had been ingested. All the procedures were carried out after obtaining informed consent. The patient has regularly eaten the tested fish thereafter, including hake. No further reactions have occurred, despite maintaining fish sensitisation (Tables 1 and 2).

IgE-mediated fish allergy has been assumed to be mostly indefinite, remaining clinically active throughout life.[1] Therefore, it usually implies a lifelong fish avoidance diet, implicating nutritional and social lifestyle restrictions. This paper reports a severe clinical case of IgE-mediated fish allergy. The patient had his first manifestations in early childhood, with anaphylactic reactions that were immediate and reproducible, after fish ingestion. The patient was sensitised to fish. Therefore, an avoidance diet was decided, without performing an OFC. After a proper fish-free diet for two years and despite positive SPT, re-introduction of fish was tried in a hospital setting. This OFC was positive after ingestion of a small portion of fish. Given the reactions' severity, the parents refused any other OFC to fish. On the following years, two more anaphylactic episodes occurred, the last one with minimal amount of fish, after a period of seven years without any known accidental exposure. SPT to fish have remained positive, except for tuna, which elicited inconsistent results over the years. Fish sIgE determination also yielded different results during follow-up but the positive values have always been rather low. When the patient was 14-years-old, he and his family specifically expressed the wish to eat fish. Our rationale for beginning fish challenges with tuna was that it appears to be one of the least allergenic species, as has been previously described.[3,5,6] One explanation for the lower allergenicity of some fish, such as tuna, can be due to its lower parvalbumin content compared to other species, since it is richer in dark muscle.[2,6] Moreover, we could demonstrate low IgE responses to tuna in our patient. After the negative tuna challenge, sole challenge was performed, also bearing in mind the low documented IgE response on testing and its lower allergenicity.[3] Although there was a slightly higher sIgE value to salmon, many of our fish allergic patients also tolerate this fish, justifying the next challenge. It is important to emphasize that these decisions were always made in agreement with the boy and his parents' decision and eating habits as we find that regular fish ingestion after negative challenges is important. Open rather than double-blind placebo controlled challenges were done as there were no previous subjective symptoms and the patient preferred it. Also identically to real life conditions, the fish was always prepared by the boy's mother. Following the same rationale, challenges with hake and cod were also performed, which were successful. These two fish were tested later, as we considered that the risk of an allergic reaction was higher. In fact, cod and hake are known to have a high parvalbumin content, being frequently responsible for symptoms in fish allergic patients,[2,3,6] and the former had caused two past anaphylactic reactions in this child. Taking into account the patient's past history of very severe reactions, we defended that all challenges had to be performed in the hospital setting, with medical supervision, and using gradually increased fish doses.

In this case report, although tolerance had already been acquired, SPT to many fish remained positive as well as the sIgE determination. These results reinforce the idea that, ultimately, OFC should be the gold standard procedure for determining the correct diagnosis and therapeutic approach. Yet, the risk of a severe reaction must always be considered. A low specificity of SPT and sIgE determination in fish allergy has been suggested. Diagnostic decision points for sIgE serum concentrations that were at least 95% predictive of clinical reactivity to fish have been established. In a prospective study, the use of 20 kU/L (CAP System – FEIA) as the cut-off point could appropriately predict clinical fish reactivity in 100% of paediatric patients.[7] The sensitivity of this cut-off point was low, indicating that it should only be used to confirm food allergy and not to exclude it. It should also be stressed that even low levels of food sIgE values are associated with a risk of clinical reactivity and these levels do not correlate with the severity of the allergic reaction.[7] The validation of the decision points has been impaired because the diagnosis of fish allergy was frequently based on convincing histories rather than OFC and the total number of studied patients was low. The utility of monitoring fish sIgE concentrations for predicting the likelihood of outgrowing fish allergy needs to be explored. To the best of our knowledge, the prognostic value of other methods in fish allergy, including the use of purified natural or recombinant allergens or techniques such as the basophil activation test, have not been published.

Reported therapeutic approaches to fish allergy may include the use of immunotherapy or desensitisation protocols. Although there have been successful reports, these are few, not largely applied or standardised.[1,8,9] Research advances such as the use of a hypoallergenic carp parvalbumin mutant or peptides mimicking allergen epitopes can be promising for safer immunotherapy against fish allergy.[1,9] Current management of fish allergy still relies on avoidance.

As there have been some reports of temporary fish tolerance (redeveloping fish allergy two and eight months after reintroducing fish, respectively),[10] our patient has continued to be monitored and keeps a therapeutic self-action plan, in case of reaction. However, we now consider unlikely that the patient will lose tolerance, as four years have passed since he began to regularly eat and tolerate fish.

In conclusion, fish allergy can be resolved, even when sensitisation and several severe immediate reactions to different fish families have occurred for a long period of time. Hence, permanent avoidance diets must be questioned. It is useful to reassess these patients' allergy status, if they are motivated and have not reacted to fish recently. A long-term follow-up may be necessary.

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