

Received: 2021.11.04

Accepted: 2022.03.25

Available online: 2022.04.15

Published: 2022.05.21

Cyclosporine A-Induced Conchal Hyperplasia with Nasal Obstruction in a Patient with Membranous Nephropathy

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 **Frank-Peter Tillmann**DEF 1 **Ana Harth**DEF 2 **Fedai Özcan**DEF 1 **Achim Jörres**

1 Department of Medicine I – Nephrology, Transplantation & Medical Intensive Care, University Witten/Herdecke, Medical Center Cologne-Merheim, Cologne, Germany

2 Department of Internal Medicine and Nephrology, University Witten/Herdecke, Dortmund, Germany

Corresponding Author: Frank-Peter Tillmann, e-mail: frank-peter.tillmann@gmx.de

Financial support: None declared

Conflict of interest: None declared

Patient: Female, 66-year-old
Final Diagnosis: Cyclosporine induced hyperplasia of the turbinates
Symptoms: Dyspnea
Medication: —
Clinical Procedure: Drug withdrawal
Specialty: Dentistry • Nephrology • Otolaryngology

Objective: Unusual clinical course

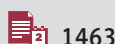
Background: The immunomodulatory and pharmacokinetic effects of cyclosporine A are used to treat diverse disease entities in different medical fields, including organ transplantation and/or autoimmune diseases. It is also applied in patients with nephrotic range proteinuria as an adjunct to steroids and supportive antihypertensive/anti-proteinuric medications. Cyclosporine has a small therapeutic window and is dosed with respect to the underlying disease entity and severity via trough level adaptations. Among its most frequent adverse effects are hypertension, nephrotoxicity, neurotoxicity, and electrolyte disturbances. Hypertrichosis and gingival hyperplasia are obvious and widely recognized adverse effects.

Case Report: We report on a 66-year-old woman who was treated with cyclosporine A for primary membranous nephropathy. During treatment with cyclosporine, she developed hirsutism and gingival hyperplasia. Later, she reported having impaired nasal breathing and dyspnea on mild physical exercise. Clinical, rhinoscopic, and radiological evaluations showed marked conchal hyperplasia as a potential cause of her symptoms. An extensive medical work-up did not show evidence of allergic, immunologic, or other drug adverse effects, suggesting cyclosporine-induced hyperplasia of the turbinates as a hypothetical causative factor. Dose reductions did not lead to resolution of symptoms but resulted in increasing proteinuria. Therefore, cyclosporine was stopped, and the patient was treated with rituximab. Thereafter, hirsutism and gingival and conchal hyperplasia gradually regressed over 2-4 months, showing complete resolution of conchal hyperplasia on computed-tomography follow-up after 6 months.

Conclusions: Cyclosporine can not only result in gingival hyperplasia but also in hyperplasia of the turbinates leading to impaired nasal breathing and shortness of breath on exertion. An extensive search for many other known causes of conchal swelling is warranted to finally suggest an adverse effect of cyclosporine. Discontinuation of cyclosporine resulted in complete remission of conchal hyperplasia as well as other adverse effects.

Keywords: Cyclosporine • Drug-Related Side Effects and Adverse Reactions • Gingival Hyperplasia • Rhinitis, Allergic • Turbinates

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/935362>



1463



—



5



12

Background

Cyclosporine A is a cyclic peptide that is used in many diverse medical fields. It is used as an immunosuppressant in transplantation medicine, but also in chronic inflammatory bowel diseases, atopic dermatitis, psoriasis, autoimmune mediated uveitis, autoimmune chronic polyarthritis, and glomerular diseases with nephrotic range proteinuria. Cyclosporine has a narrow therapeutic window. As a result, drug dosing is dependent on the underlying clinical disease entity and individualized according to morning trough levels. Possible adverse effects, among many others, are hypertension, hirsutism, oedema, or gingival hyperplasia. Although the adverse effects described above have been known for many years, no predisposing risk factors have been described so far in drug-naïve patients. When corresponding adverse effects occur, various therapeutic procedures have been applied besides adaptations of trough levels as first action, such as an extension of antihypertensive therapy in case of worsening of hypertension, laser surgical procedures in case of hirsutism or gingival hyperplasia, a switch to tacrolimus, or a complete discontinuation of cyclosporine medication. Whereas cyclosporine A-induced gingival hyperplasia presents with a pathognomonic clinical picture and is generally well known as an adverse effect of cyclosporine A, most of the other adverse effects are usually diagnoses of exclusion in routine clinical practice [1].

Case Report

Hereby, we report on a 66-year-old non-smoking woman who was treated with cyclosporine A as part of a drug regimen for recurrent proteinuria due to primary membranous nephropathy. The initial clinical course of the glomerulonephritis was characterized by sudden increases in proteinuria with slow reduction and finally complete resolution during 6-12 months on antihypertensive therapy alone, consisting mainly of strict blood pressure control using blockers of the renin-angiotensin-aldosterone-system as a mainstay of the drug regimen. Further medications consisted only of low-dose prednisolone and calcidiol to treat secondary hypovitaminosis. After 3 relapses, cyclosporine A was introduced to the regimen to accelerate the decline of proteinuria and to prevent or delay a further relapse. Six months after the introduction of cyclosporine A, the patient developed mild hirsutism and gingival hyperplasia (Figure 1). She also reported feeling a nasal obstruction with impaired nasal breathing associated with dyspnea, even during light physical exertion such as climbing stairs, and disturbed sleep at night. Besides gingival hyperplasia and mild hirsutism, no other remarkable signs were found on clinical examination. Especially, there were no signs of nasal discharge or infectious rhinitis, nor did the patient report having chronic rhinitis in the past. The past medical history



Figure 1. A 66-year-old female patient with gingival hyperplasia due to cyclosporine A medication as part of a multi-drug regimen for membranous nephropathy.

was also unremarkable with respect to increased allergic reactions. The mean cyclosporine trough level over the whole treatment course was 86 ng/ml (min 52; max 148 ng/ml, 92 ng/ml at presentation) and the estimated glomerular filtration rate at first CT-evaluation was 65 ml/min/1.73 m² body surface area (BSA). There were no laboratory signs of infections, disturbed thyroid function, peripheral blood eosinophilia, or local or systemic vasculitis such as ANCA-associated disease entities. An ear-nose-throat (ENT) examination did not reveal any indicative cause, but rhinoscopic and computed-tomography (CT) of the head showed evidence of a pronounced nasal conchal hyperplasia (Figures 2, 3). Although there were no indications of an allergic cause clinically and anamnestically, alongside with a normal IgE antibody titer, topical therapy with cortisone was carried out without any effect on the conchal hyperplasia. As an extensive search for other causes of the hyperplastic turbinates (pharmacological, allergic, and autoimmune) was unremarkable, biopsy of the nasal mucosa was discussed but discarded because of potential risks. In addition, the benefit of bioptically evaluating the hyperplastic conchae was seen as controversial, as progressive gingival hyperplasia also suggested a therapeutic omission of cyclosporine medication from a dental and dermatological perspective. As the patient remained proteinuric and dyspneic, medication with cyclosporine A was discontinued and rituximab was introduced (4 times 375 mg/m² BSA) to treat membranous nephropathy, inducing a lasting remission of proteinuria and anti-phospholipase-2-receptor autoantibodies. Thereafter, the hirsutism and gingival hyperplasia slowly resolved over several months and a CT-radiologic control showed complete resolution of turbinate hyperplasia (Figures 4, 5). On last follow-up visit, the patient was free of immunomodulatory medications and had normal renal function without signs of proteinuria and/or albuminuria on urine analysis. After the cyclosporine medication was discontinued, no signs of nasal obstruction or mucosal swelling have reoccurred so far.

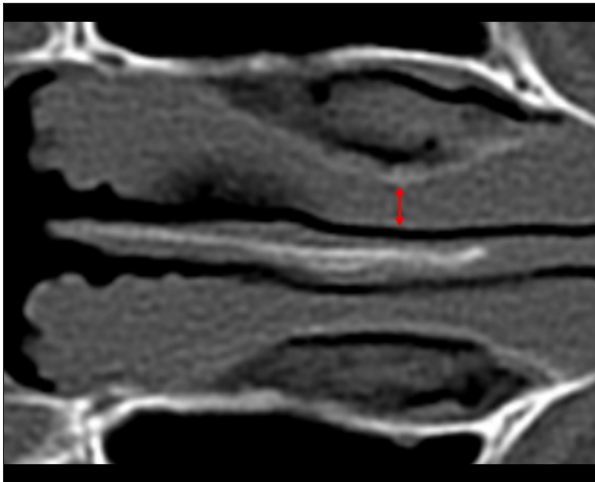


Figure 2. CT scan under cyclosporine A medication showing hyperplastic turbinates of 3.7 mm.

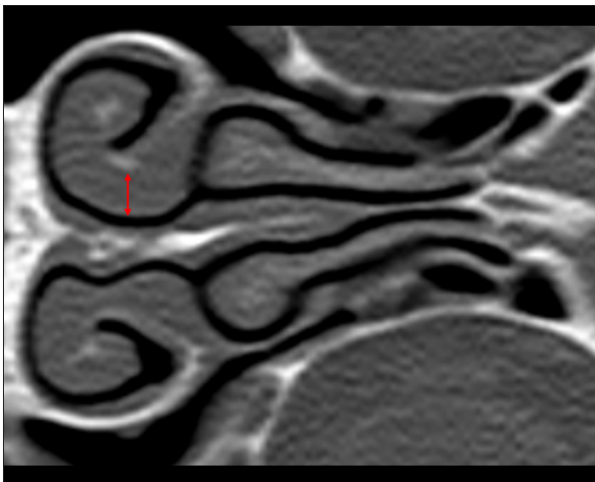


Figure 3. CT scan under cyclosporine A medication showing hyperplastic turbinates of 4.2 mm.

Discussion

Cyclosporine A is a cyclic peptide isolated in 1971 from the Norwegian tubular fungi *Tolypocladium inflatum* and *Cylindrocarpum lucidum*. Its immunomodulatory properties were first described in 1976 [1]. The broad application of the drug in various disciplines such as transplantation medicine, gastroenterology, dermatology, rheumatology, nephrology, and other fields requires a good knowledge of potential adverse effects. In this regard, nephrotoxic and neurotoxic effects, disturbances of the electrolyte or acid-base balance, and glucose homeostasis, worsening of arterial hypertension, dyslipidemia, gingival hyperplasia, and hirsutism have been described so far [3]. Our patient had already developed mild gingival hyperplasia and hirsutism as adverse effects. However, there were no other known adverse effects detected. Hyperplasia of the gingival mucosa can lead to massive bleeding as well as loss of

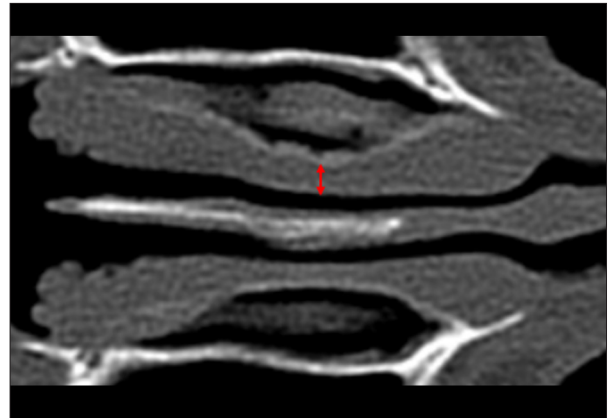


Figure 4. CT scan showing regression of hyperplasia 6 months after discontinuation of cyclosporine A. The diameter at a corresponding anatomical location as compared to the baseline scan was 2.6 mm.

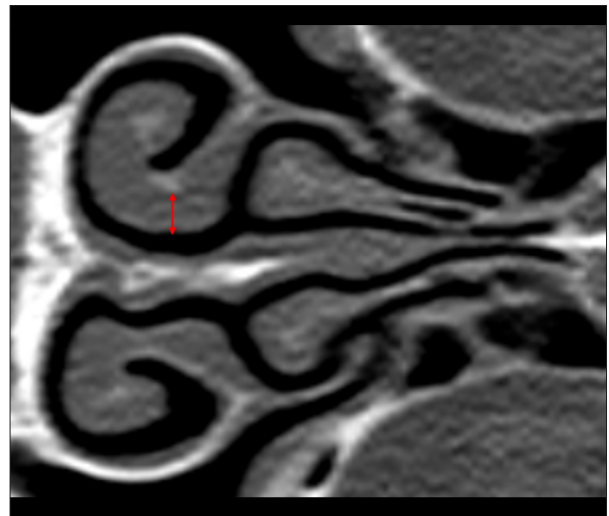


Figure 5. CT scan showing regression of hyperplasia 6 months after discontinuation of cyclosporine A. The diameter at a corresponding anatomical location as compared to the baseline scan was 2.8 mm.

teeth [4]. Therefore, the patient underwent regular oral surgical control, and a single resection of the hyperplastic gingiva using a diode laser was performed [5]. Many drugs affecting the autonomic nervous system have been reported to potentially cause nasal obstruction [6,7]. One main mechanism of action described refers to the capacity of these medications to dilate nasal vessels with consecutive swelling, edema, and in some cases rhinorrhea. Although not present in our patient, cyclosporine has been associated with flush symptoms, but major vasoconstrictive properties with constriction of the afferent arteriole of the glomerulus are known to be responsible for major renal adverse effects [8]. These effects seem to be partly mediated via decreased production of endothelial prostaglandin E2 and nitric oxide [9]. Other mechanisms of adverse

effects include formation of a cyclosporine-cyclophilin complex that subsequently inhibits the dephosphorylation activity of the phosphatase calcineurin, reductions in Na⁺/K⁺-ATPase pump activity in the medullary thick ascending limb of the loop of Henle and cortical collecting duct, reduced renal TRPV5 expression, reduced renal magnesium reabsorption, and interference with 'nuclear factor of activated T cells' proteins signaling in pancreatic B cells with decreased insulin secretion [1]. High peak levels of cyclosporine have been associated with severe neurologic toxicity [10]. Recent in vitro studies indicate that the cause of mucosal hyperplasia might be assumed in a cyclosporine A-induced disturbance of the synthesis of proteases in fibroblasts with consecutive accumulation of extracellular matrix components [11]. Although no hyperplastic turbinates have been described with cyclosporine A medication so far, the presumed pathophysiology suggests the occurrence of hyperplastic mucosa in anatomical areas other than the gingiva. Many other drugs have been reported to potentially cause turbinate hyperplasia [6,7], but none of these could be responsible for the symptoms in this case. At the time of diagnosis, the patient was not receiving any of these medications with similar adverse effects on the mucous membranes, especially calcium antagonists or other antihypertensives [12]. Additionally, there was no evidence of an acute or chronic allergic cause or nasal discharge (evaluated in depth on ENT specialist examination). Dose reductions did not result in satisfactorily reductions in adverse effects, but resulted in increasing proteinuria. Therefore, the patient was switched to a rituximab-based immunosuppressive regimen and cyclosporine A medication was stopped completely. After discontinuation of cyclosporine, the symptoms gradually improved over 2 months and finally resolved completely. In our opinion, this fact, in combination with CT-radiologically-proven complete regression of the turbinate hyperplasia, speak in favor of a potential rare drug adverse effect as the cause of the

conchal mucus membrane swelling. To the best of our knowledge, this is the first case report of cyclosporine A-induced hyperplasia of the turbinate mucosa. In case of corresponding symptoms, a CT-radiological confirmation of the diagnosis should be sought in addition to an ENT medical examination. Further investigations are necessary to elucidate the incidence of this currently unrecognized adverse effect.

Limitations

A major limitation of this case report is the lack of strong evidence of an actual cyclosporine A-induced cause of the conchal hyperplasia. Nevertheless, in our opinion there are so far no other means to definitively prove this hypothesis. Instead, we relied on a diagnosis of exclusion in this hypothesis-generating case report.

Conclusions

Cyclosporin A is often used as part of an immunomodulatory therapy in diverse medical fields. In the case of corresponding symptoms, this case raises the hypothetical, unproven possibility of cyclosporin A-induced turbinate hyperplasia, and we suggest considering this as an extremely rare potential cause in the differential work-up of respective cases. Nevertheless, this entity, if supported in further investigations, will remain a diagnosis of exclusion warranting thorough prior diagnostic work-up.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Patocka J, Nepovimova E, Kuca K, Wu W. Cyclosporine A: Chemistry and toxicity – a review. *Curr Med Chem*. 2021;28:3925-34
2. Borel JF, Feurer C, Gubler HU, Stahelin H. Biological effects of cyclosporine A: a new antilymphocytic agent. *Agents Actions*. 1976;6:468-75
3. Farouk SS, Rein JL. The many faces of calcineurin inhibitor toxicity – what the FK? *Adv Chronic Kidney Dis*. 2020;27:56-66
4. Gandhi M, Rai E, Shirley A, Suda NK. Massive gingival bleed: A rare manifestation of cyclosporine toxicity. *BMJ Case Rep*. 2020;13:e236828
5. Aral CA, Dilber E, Aral K, et al. Management of cyclosporine and nifedipine-induced gingival hyperplasia. *J Clin Diagn Res*. 2015; 9:ZD12-15
6. Cingi C, Ozdoganoglu T, Songu M. Nasal obstruction as a drug side effect. *Ther Adv Respir Dis*. 2011;5:175-82
7. Mabry RL. Nasal stuffiness due to systemic medications. *Otolaryngol Head Neck Surg*. 1983;91:93-94
8. Curtis JJ, Luke RG, Dubovsky E, et al. Cyclosporin in therapeutic doses increases renal allograft vascular resistance. *Lancet*. 1986;2:477-79
9. De Nicola L, Thomson SC, Wead LM, et al. Arginine feeding modifies cyclosporine nephrotoxicity in rats. *J Clin Invest*. 1993;92:1859-65
10. Bechstein WO. Neurotoxicity of calcineurin inhibitors: Impact and clinical management. *Transpl Int*. 2000;13:313-26
11. Lauritano D, Palmieri A, Lucchese A, et al. Role of cyclosporine in gingival hyperplasia: An in vitro study on gingival fibroblasts. *Int J Mol Sci*. 2020;21:595
12. Wynn RL. Calcium channel blockers and gingival hyperplasia – an update. *Gen Dent*. 2009;57:105-7