A Supraglottic Pseudotumor in an Immunocompromised Patient with Nephrotic Syndrome, Herpes Zoster, and a Cytomegalovirus Infection

Tetsu Akimoto, Tomoyuki Yamazaki, Osamu Saito, Shigeaki Muto, Eiji Kusano and Daisuke Nagata

Division of Nephrology, Department of Internal Medicine, Jichi Medical University, Shimotsuke-Shi, Tochigi, Japan.

ABSTRACT: Several viral infections may occasionally induce supraglottic mass lesions, resulting in an obstructive airway emergency. We herein report one such case in a 63-year-old male immunocompromised patient with nephrotic syndrome due to membranous nephropathy who also had ophthalmic herpes zoster with a laryngeal mass, which required urgent intubation and mechanical ventilation. The patient was initially treated with acyclovir; however, because a serological analysis revealed a concurrent cytomegalovirus infection, we discontinued the administration of acyclovir and gave priority to the simultaneous treatment of the cytomegalovirus and varicella-zoster virus infections with ganciclovir. The clinical course was favorable, and he was weaned from the ventilator 10 days later when a serial imaging analysis revealed no signs of the supraglottic mass, leading us to conclude that these two viral infections could have additively or synergistically contributed to the development of the local pseudotumor. The diagnostic and therapeutic concerns arising in the current case are also discussed.

KEYWORDS: nephrotic syndrome, herpes zoster ophthalmicus, laryngeal mass, steroid, cytomegalovirus

CITATION: Akimoto et al. A Supraglottic Pseudotumor in an Immunocompromised Patient with Nephrotic Syndrome, Herpes Zoster, and a Cytomegalovirus Infection. *Clinical Medicine Insights: Case Reports* 2016:9 61–65 doi: 10.4137/CCRep.S40058.

TYPE: Case Report

RECEIVED: May 18, 2016. **RESUBMITTED:** June 30, 2016. **ACCEPTED FOR PUBLICATION:** July 05, 2016.

ACADEMIC EDITOR: Athavale Nandkishor, Associate Editor

PEER REVIEW: Three peer reviewers contributed to the peer review report. Reviewers' reports totaled 655 words, excluding any confidential comments to the academic editor.

FUNDING: This study was supported in part by a Grant-in-Aid for Research on Advanced Chronic Kidney Disease, Practical Research Project for Renal Diseases from Japan Agency for Medical Research and Development, AMED. The authors confirm that the funder had no influence over the study design, content of the article, or selection of this journal.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

CORRESPONDENCE: tetsu-a@jichi.ac.jp

Introduction

Viral and virally associated diseases show various head and neck manifestations.[1] Such pathologies may occasionally induce supraglottic mass lesions, resulting in an obstructive airway emergency.[2] We herein report one such case in which a male immunocompromised patient with nephrotic syndrome due to membranous nephropathy (MN) and ophthalmic herpes zoster (HZ), a phenotype of HZ that develops in patients presenting with the reactivation of latent varicella-zoster virus (VZV) in the ophthalmic division of the trigeminal nerve,[3–6] developed a laryngeal mass that required urgent intubation and mechanical ventilation. The patient has given consent for publication of information and images in this report.

Case Report

A 63-year-old male patient whose condition was complicated by nephrotic syndrome presented with a five-day history of severe right periorbital edema with eruption of blisters over the ipsilateral forehead (Fig. 1A). Nineteen months prior to his presentation, he was found to have the nephrotic syndrome due to biopsy-proven MN. He was then started on oral prednisolone (PSL) at a dose of 50 mg/day, which was titrated thereafter at doses that ranged from 10 to 40 mg/day, depending on the context. Ten months after the renal biopsy, oral cyclosporine A (CyA; 100 mg/day) was added to the therapeutic regimen. Nonetheless, he never reached even a partial remission, and his nephrotic-range proteinuria of approximately 7–10 g/day persisted and his renal function steadily and progressively declined. Oral PSL (35 mg/day) and CyA (100 mg/day) were therefore administered in combination with oral trimethoprim–sulfamethoxazole (160 mg of trimethoprim and 800 mg of sulfamethoxazole per week) as antimicrobial prophylaxis during the last four weeks prior to the presentation. In this period, his peripheral lymphocyte counts were around 600–800/μL. A Tzanck smear test of the vesicular lesions revealed multinucleated giant cells, while he also complained of a sore throat associated with odynophagia and burning pain in the right cervical area with an erythematous patch (Fig. 1B). He was subsequently admitted to our hospital for a further workup. At that time, a cumulative oral PSL dose of 13.1 g had been administered. Physical examination revealed that he had anasarca, and his height was 167 cm and weight was 65.2 kg. Laboratory examinations revealed the following results: white blood cell count, 15,700/μL (neutrophils, 92.3%; lymphocytes, 1.1%; monocytes, 4.6%; eosinophils, 0.8%; and basophils, 1.2%); hemoglobin, 14.0 g/dL; platelet count, 20×10^4/μL; blood urea nitrogen, 77 mg/dL; creatinine (Cr), 4.23 mg/dL;

total protein, 4.6 g/dL, albumin (Alb), 2.5 g/dL; C-reactive protein, 0.3 mg/dL; immunoglobulin (Ig) G, 311 mg/dL; IgA, 163 mg/dL; and IgM, 18 mg/day. Within a few hours after admission, he gradually developed dyspnea with stridor. A computed tomography (CT) scan showed the presence of a supraglottic mass (Fig. 1C), while endoscopy revealed a right laryngeal space-occupying lesion involving the false vocal cord and aryepiglottic fold filling the right pyriform sinus, thereby causing almost complete airway obstruction. The patient was then intubated to secure his airway and placed on a mechanical ventilator. He was presumptively diagnosed as having HZ ophthalmicus (HZO) with laryngeal involvement. The administration of CyA was stopped and tapering of PSL was commenced, after which treatment with intravenous acyclovir (ACV; 400 mg/day) combined with broad-spectrum antibiotics was started empirically. The patient was also subjected to hemodialysis (HD) treatment three times a week to strictly control his volume status. The elevation of serum titers of both anti-VZV IgM (IgM index 2.9, cut-off index 0.8) and IgG (3,400 IU/mL) was confirmed on hospital day 6 after the patient's admission, at which time a cytomegalovirus (CMV) antigenemia (CMV-Ag) assay with monoclonal antibodies C10/C11 revealed that the patient also had a CMV infection. The patient had an increased number of CMV-antigen-positive leukocytes (27/36), a lymphocyte count of 400/μL, and a CD4 T-lymphocyte count of 152/μL. We then discontinued the administration of ACV and gave priority to the simultaneous treatment of the CMV and VZV infections with intravenous ganciclovir (GCV; 1.29 mg/kg) thrice a week (Fig. 2), although this agent is not the first-line treatment for VZV-related disease.[7] The patient was subsequently weaned from the ventilator by hospital day 10 when a serial CT scan revealed no signs of the supraglottic mass. On hospital day 24, the CMV antigen assay became negative and the administration of GCV was terminated, as the cutaneous lesions around the orbital area subsided and the cervical erythema disappeared completely. Around the same time, an arteriovenous fistula (AVF) was created in the left forearm and the periodic HD program was continued. Overall, the patient's clinical course was favorable, and the oral PSL treatment was withdrawn approximately nine weeks after admission. At one-year follow-up, continued symptomatic

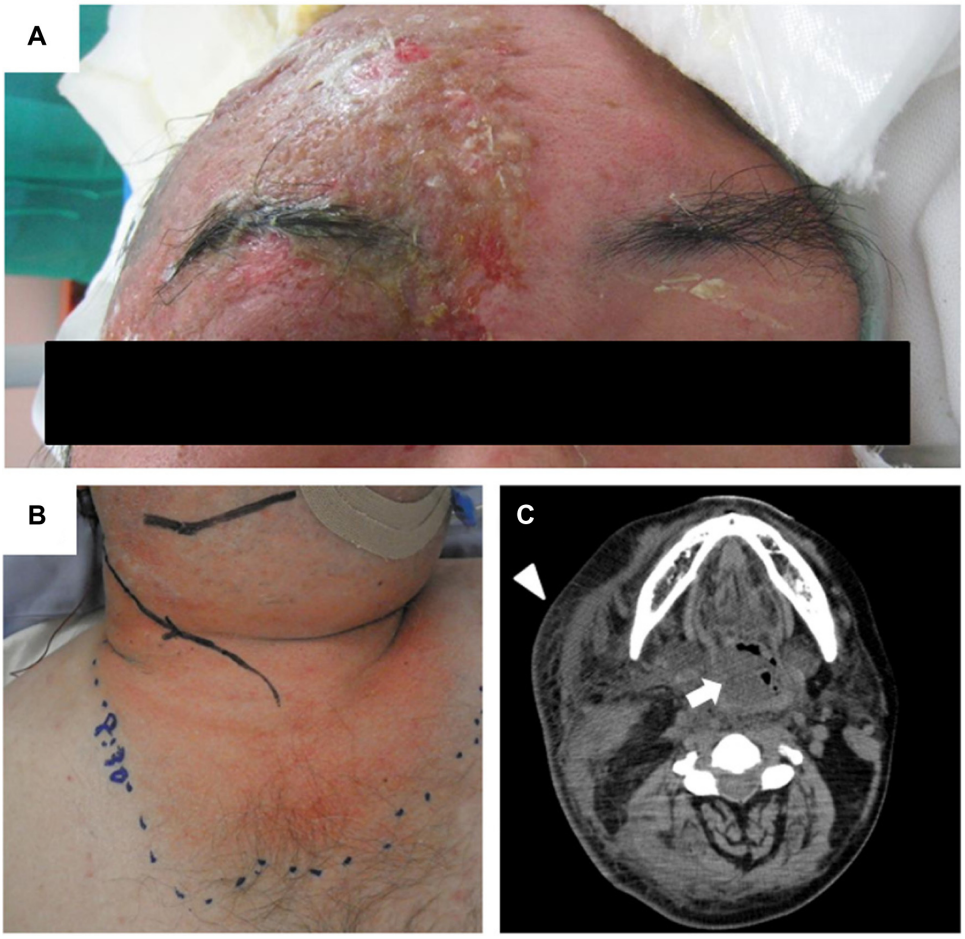

Figure 1. (**A**) A photo obtained on hospital day 5 showing a tender erythematous, vesicular, crusting lesion on the right periorbital skin. (**B**) An erythematous patch without a vesicular rash over the perilaryngeal skin just after intubation. (**C**) Axial CT of the neck demonstrating an expansive lesion in the right supraglottic region (arrow). Note that diffuse reticulation of subcutaneous fat was detected in the right cervical territory, suggesting cellulitic inflammation (arrowhead).

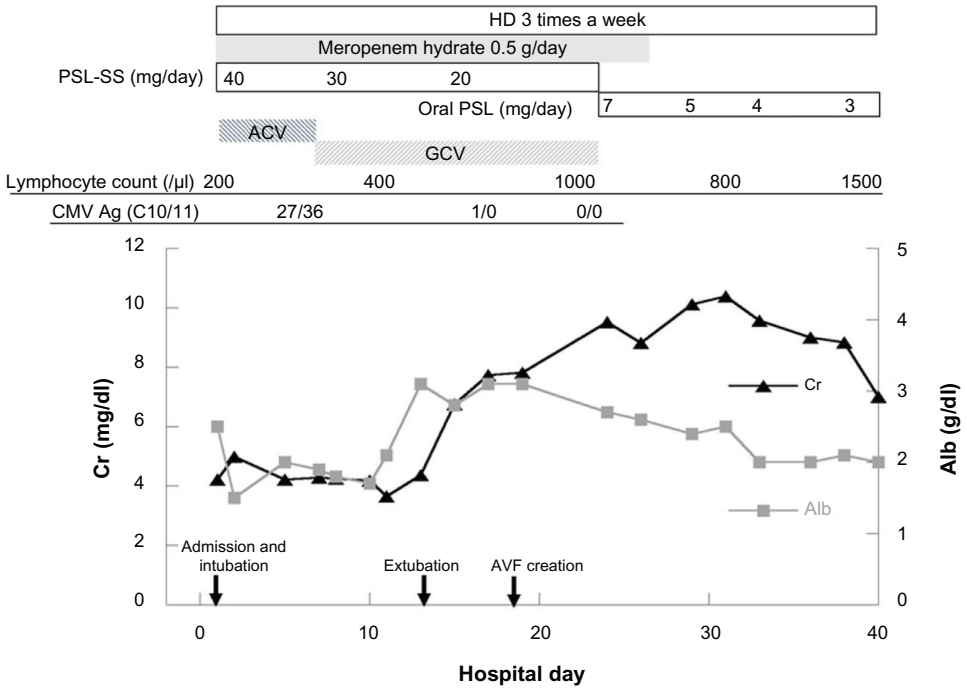

Figure 2. The clinical course of the current patient. From the point of admission, which was designated as hospital day 1, the orally administered PSL was transiently switched to the intravenous PSL sodium succinate (PSL-SS). The resumed oral PSL was tapered thereafter and subsequently terminated. After starting the HD treatment for the deteriorated renal function as well as strict volume control, his daily urine volume gradually decreased, while his serum levels of Cr were finally settled around 8–10 mg/dL.

management with pregabalin was required for persistent postherpetic neuralgia.

Discussion

HZ is a neurocutaneous disease that results from the reactivation of latent VZV infection within the cranial or dorsal root ganglia.[3] Reactivation of dormant VZV is associated with the waning of cell-mediated immunity, either as a natural consequence of aging or as a result of immunosuppression.[3,4] The fact that the deoxyribonucleic acid of VZV is detected in the trigeminal, cervical, thoracic, lumbar, and sacral dorsal root ganglia in autopsy studies implies that VZV remains latent in most sensory dorsal root ganglia.[8] The segmental nature of HZ may therefore depend on the VZV genome load distribution in different dorsal root ganglia, with the highest viral genome load leading to a characteristic dermatomal rash,[9,10] while zoster may present in a multidermatomal fashion in some subsets of patients with an immunosuppressed status.[5,10] Obtaining the diagnosis of HZO in the current case was straightforward after confirming the characteristic manifestations, including a unilateral painful maculopapular rash with vesicles, crusting, ulceration, and erythematous edema on the forehead and periocular region.[3,6] Although one may argue that such a clinical picture may be too common to be described in the literature, the significance of our experience should be evaluated more carefully in terms of the concurrent development of a laryngeal mass that resulted in airway narrowing severe enough to require urgent intubation. Although malignancy is the greatest concern in subjects presenting with neck masses,[11] we believe that some inflammatory and/or infective processes, which may resolve with conservative treatment and in which the lesions are seldom removed or biopsied,[12] may have played a role in the development of the disease in the current patient.

Laryngeal zoster, a phenotype of HZ in the head and neck, includes a wide spectrum of manifestations, such as laryngeal mucosal eruptions, skin erythema, and multiple cranial nerve palsies.[13–17] VZV reactivation in the larynx may also mimic neoplasms by presenting with laryngeal masses,[18–20] and cases of laryngeal zoster without motor disorders or mucosal lesions are not exceptional.[14,16,21] Therefore, the laryngeal mass in the current patient can be attributed to a VZV-dependent mechanism, and it is thus not surprising that we failed to confirm any signs suggestive of laryngeal paresis, such as hoarseness or dysphagia, on the initial presentation, in addition to mucosal eruptions. Considering the innervation of the laryngeal area, the concurrent VZV reactivation with vagus nerve involvement may have played a role,[13,18,20] at least in part, in the establishment of the cervical manifestations in the current patient. Despite the absence of a vesicular rash, the detection of a tender erythematous patch over the perilaryngeal skin, which did not accord with the dermatomal distribution in the cervical region, may be a subtype of a cutaneous manifestation of presumable vagal VZV mononeuritis, as described by Wu et al.[13] Otherwise, one may argue that the involvement of a bacterial infectious process, such

as paralaryngeal abscess formation, cannot be excluded. Alternatively, or in addition, we should need to focus on the concurrent CMV infection as another potential etiology for the disease. Indeed, cases of CMV-associated laryngeal masses have been reported anecdotally.[22,23] Although the diagnostic impact of such a manifestation of CMV disease remains to be delineated, it has been previously stressed that invasive CMV infection in immunocompromised patients may start as a self-limited infection in the upper airway.[22] Our failure to perform surgical and histological assessments precludes us from pursuing the differential diagnosis for the neck mass thoroughly. Nevertheless, it is reasonable to consider that these two viral infections could have additively or synergistically contributed to the prominent local pseudotumor. The prompt response of the tumor lesion to GCV that was observed in the current case strongly supports our proposal. However, this agent has been anecdotally shown to have a clinical benefit in the treatment for VZV infection.[7]

MN is one of the most common causes of nephrotic syndrome in adult subjects.[24] The role of corticosteroids and various immunosuppressive agents as the basic treatment for this disease is still a matter of debate,[24–27] and it is thus not surprising that our patient finally progressed to end-stage renal failure along with a persistent nephrotic condition, despite the application of a therapeutic regimen consisting of PSL and CyA. This case may rather concern regarding how to deal with various types of steroids and immunosuppressants in patients with concurrent viral and/or bacterial infection. It has been shown that corticosteroids are beneficial and safe for a wide variety of infections,[28] while the discontinuation and/or tapering of immunosuppressive regimens is an accepted option in this patient with active infections due to their immunosuppressive nature.[29,30] The paucity of information regarding these points in nephrotic patients with MN complicated by HZ and CMV infections implies that numerous decisions as to whether to continue immunosuppressive management are potentially empirical, as in the present patient. Considering the diverse etiologies of an immunocompromised status,[31] the establishment of standardized strategy regarding therapeutic immunomodulation is challenging. However, we are of the opinion that a careful analysis of all of the options and the risk of severe infections as well as disease severity on a case-by-case basis should be mandatory. Needless to say, setting up an appropriate microbial diagnosis is another prerequisite as the list of potential microbial invaders in the immunocompromised milieu is broad, and antimicrobial strategies may differ according to the various clinical settings.[32] Finally, our experience stresses the importance of having a high index of suspicion, with prompt recognition and immediate intervention for obstructive airway emergencies caused by concurrently developing laryngeal masses, which can be associated with ophthalmic HZ and CMV infection as diagnostic and therapeutic challenges beyond the field of nephrology, thereby reducing and preventing the incidence of morbidity of the disease.

Author Contributions

Drafted the manuscript: TA, TY. Made contributions to the acquisition of the clinical data: TY, OS. Provided a detailed review of the contents and structure of the manuscript, resulting in significant changes to the original document: SM, EK, DN. All the authors have read and approved the final manuscript.

REFERENCES

1. Montone KT. Infectious diseases of the head and neck: a review. *Am J Clin Pathol*. 2007;128(1):35–67.
2. Sanei-Moghaddam A, Loizou P, Fish BM. An unusual presentation of herpes infection in the head and neck. *BMJ Case Rep*. 2013;2013:bcr2012007928.
3. Weinberg JM. Herpes zoster: epidemiology, natural history, and common complications. *J Am Acad Dermatol*. 2007;57(6 suppl):S130–5.
4. Weaver BA. Herpes zoster overview: natural history and incidence. *J Am Osteopath Assoc*. 2009;109(6 suppl 2):S2–6.
5. Gross G, Schöfer H, Wassilew S, et al. Herpes zoster guideline of the German Dermatology Society (DDG). *J Clin Virol*. 2003;26(3):277–89.
6. Liesegang TJ. Herpes zoster ophthalmicus natural history, risk factors, clinical presentation, and morbidity. *Ophthalmology*. 2008;115(2 suppl):S3–12.
7. Aitken C, Hawrami K, Miller C, Barrett Muir W, Yaqoob M, Breuer J. Simultaneous treatment of cytomegalovirus and varicella zoster infections in a renal transplant recipient with ganciclovir: use of viral load to monitor response to treatment. *J Med Virol*. 1999;59(3):412–4.
8. Kennedy PG, Cohrs RJ. Varicella-zoster virus human ganglionic latency: a current summary. *J Neurovirol*. 2010;16(6):411–8.
9. Pevenstein SR, Williams RK, McChesney D, Mont EK, Smialek JE, Straus SE. Quantitation of latent varicella-zoster virus and herpes simplex virus genomes in human trigeminal ganglia. *J Virol*. 1999;73(12):10514–8.
10. Takaoka Y, Miyachi Y, Yoshikawa Y, Tanioka M, Fujisawa A, Endo Y. Bilateral disseminated herpes zoster in an immunocompetent host. *Dermatol Online J*. 2013;19(2):13.
11. Gleeson M, Herbert A, Richards A. Management of lateral neck masses in adults. *BMJ*. 2000;320(7248):1521–4.
12. Balikci HH, Gurdal MM, Ozkul MH, et al. Neck masses: diagnostic analysis of 630 cases in Turkish population. *Eur Arch Otorhinolaryngol*. 2013;270(11):2953–8.
13. Wu CL, Linne OC, Chiang CW. Herpes zoster laryngis with prelaryngeal skin erythema. *Ann Otol Rhinol Laryngol*. 2004;113(2):113–4.
14. Watelet JB, Evrard AS, Lawson G, et al. Herpes zoster laryngitis: case report and serological profile. *Eur Arch Otorhinolaryngol*. 2007;264(5):505–7.
15. Van Den Bossche P, Van Den Bossche K, Vanpoucke H. Laryngeal zoster with multiple cranial nerve palsies. *Eur Arch Otorhinolaryngol*. 2008;265(3):365–7.
16. Morinaka S. Herpes zoster laryngitis with intractable hiccups. *Auris Nasus Larynx*. 2009;36(5):606–8.
17. Lin YY, Kao CH, Wang CH. Varicella zoster virus infection of the pharynx and larynx with multiple cranial neuropathies. *Laryngoscope*. 2011;121(8):1627–30.
18. Pinto JA, Pinto HC, Ramalho Jda R. Laryngeal herpes: a case report. *J Voice*. 2002;16(4):560–3.
19. Higuchi E, Nakamaru Y, Ohwatari R, et al. Laryngeal zoster mimicking a laryngeal cancer. *Otolaryngol Head Neck Surg*. 2005;133(4):647.
20. Shihada R, Brodsky A, Luntz M. Laryngeal mass with multiple cranial neuropathies as a presenting sign for varicella zoster infection. *Dysphagia*. 2010;25(2):153–5.
21. Chitose SI, Umeno H, Hamakawa S, Nakashima T, Shoji H. Unilateral associated laryngeal paralysis due to varicella-zoster virus: virus antibody testing and videofluoroscopic findings. *J Laryngol Otol*. 2008;122(2):170–6.
22. Tinelli M, Castelnuovo P, Panigazzi A, D'Andrea F, Caprioglio S. Mass lesions of the larynx due to cytomegalovirus infection in a patient infected with the human immunodeficiency virus. *Clin Infect Dis*. 1995;20(3):726–7.
23. Friedman AD, Maurer WG, Byrd MC, Cook JR, Lorenz RR. A cytomegalovirus-associated mass presenting with laryngeal obstruction. *Arch Otolaryngol Head Neck Surg*. 2006;132(12):1375–8.
24. Polanco N, Gutiérrez E, Covarsí A, et al. Spontaneous remission of nephrotic syndrome in idiopathic membranous nephropathy. *J Am Soc Nephrol*. 2010;21(4):697–704.
25. Akimoto T, Otake T, Tanaka A, et al. Steroid treatment in patients with membranous nephropathy and hepatitis B virus surface antigenemia: a report of two cases. *Clin Exp Nephrol*. 2011;15(2):289–93.

26. Aaltonen S, Honkanen E. Outcome of idiopathic membranous nephropathy using targeted stepwise immunosuppressive treatment strategy. *Nephrol Dial Transplant*. 2011;26(9):2871–7.
27. Usui J, Hirayama K, Suzuki S, Koyama A, Yamagata K. Combined administration of low-dose prednisolone and cyclosporine in idiopathic membranous nephropathy: Tsukuba's regimen for IMN. *Clin Exp Nephrol*. 2012;16(4):654–5.
28. McGee S, Hirschmann J. Use of corticosteroids in treating infectious diseases. *Arch Intern Med*. 2008;168(10):1034–46.
29. Mañez R, Kusne S, Linden P, et al. Temporary withdrawal of immunosuppression for life-threatening infections after liver transplantation. *Transplantation*. 1994;57(1):149–51.
30. Wiegering V, Schick J, Beer M, et al. Varicella-zoster virus infections in immunocompromised patients – a single centre 6-years analysis. *BMC Pediatr*. 2011;11:31.
31. Mahon JL, Stiller CR. The immunocompromised patient. *Can Fam Physician*. 1987;33:349–59.
32. Sonesson A, Oqvist B, Hagstam P, Björkman-Burtscher IM, Miörner H, Petersson AC. An immunosuppressed patient with systemic vasculitis suffering from cerebral abscesses due to *Nocardia farcinica* identified by 16S rRNA gene universal PCR. *Nephrol Dial Transplant*. 2004;19(11):2896–900.