ORIGINAL ARTICLE

Cutaneous viral infections in patients after kidney transplantation: risk factors

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KEY WORDS

cutaneous viral infections, immunosuppression, kidney transplantation, risk factors for infection

ABSTRACT

INTRODUCTION Infectious skin lesions are a common complication in renal transplant patients receiving immunosuppressive therapy.

OBJECTIVES The aim of this study was to assess the prevalence and factors contributing to the development of viral skin infections in kidney transplant patients.

PATIENTS AND METHODS The study included 486 patients, 296 men (60.9%) and 190 women (39.1%), aged 46.1 ±13.1 years, 74.3 ±52.1 months post-transplantation, who remained mostly on triple immunosuppressive therapy. All skin lesions detected during the dermatological examination were described in detail, and the type, size, exact location, dependence on age, sex, and the used immunosuppressive therapy were established. Patients were followed for 5 years.

RESULTS Infectious skin lesions of viral origin were diagnosed in 189 of 486 patients (38.9%). The most frequent infections were viral warts (38.5%), which were more common in older patients (47.6 vs. 45.0 years, $P < 0.033$). Viral warts were observed more often in men ($P < 0.031$). Lesions of viral origin occurred more often in patients treated with immunosuppressive drugs for a longer period of time (53 vs. 37 months; $P < 0.021$) and those who received azathioprine and cyclosporine A ($P < 0.001$). In a multivariate logistic regression analysis, therapy with azathioprine was the only factor associated with increased risk of these complications ($P < 0.007$).

CONCLUSIONS Older age, male sex, and longer duration of immunosuppressive therapy affect the incidence of infectious skin lesions in patients after kidney transplantation. Treatment with cyclosporine A and azathioprine promotes the development of infectious viral warts.

INTRODUCTION Chronic kidney disease (CKD) is a worldwide underdiagnosed health problem with increasing incidence and prevalence that worsens the prognosis mainly because of an elevated risk of cardiovascular events and mortality.[1] Although kidney transplantation is the best treatment option for patients with end-stage CKD, organ recipients suffer from numerous clinical problems.[2,3] The prolonged use of immunosuppressive drugs predisposes graft recipients to infectious diseases and virus-related malignancies.[4] Transplant recipients experience a nearly 2-fold elevated risk for all types of de novo cancers, while oncogenic virus infections increased the risk of cancer up to 100-fold.[4,5] There is some evidence that seborrheic warts and verrucokeratotic cutaneous lesions are strongly associated with the risk of squamous cell carcinoma, while verruce vulgaris and flat warts are not.[6,7]

Viral skin infections are the most common complications that decrease the quality of life in organ recipients.[8] The therapeutic management of infections in patients treated with immunosuppressive drugs is usually disappointing.[8-10]

The used immunosuppressive drugs block the most important stage in antiviral defense, which is a cytotoxic T-lymphocyte HLA-dependent response. This favors the reactivation of latent infections, the development of new, enhanced virus replication and promotes generalization of the infection.[11]

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Received: August 26, 2013.
Revision accepted: September 25, 2013.
Published online: September 26, 2013.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2013; 123 (12): 686-692

Cutaneous viral infections are the most common lesions observed in patients after transplantation and they usually result from reactivation of previous infection.

The aim of the study was to assess the type of infectious skin lesions of viral etiology and the factors contributing to their occurrence in patients after kidney transplantation.

PATIENTS AND METHODS The study included 486 patients, 296 men (60.9%), and 190 women (39.1%) aged 46.0 ±13.1 years (range, 18–74 years) who underwent kidney transplantation from deceased donors in Kraków and other centers in Poland and who remained under the supervision of an outpatient clinic for transplant patients at the Department of Nephrology, University Hospital. In the analyzed group, 480 patients received the first graft and 6 had the second graft.

The most common cause of renal failure in this group was chronic glomerulonephritis.

A total of the 392 evaluable patients (80.7%) were treated before transplantation by hemodialysis and 78 patients (16.0%) by peritoneal dialysis (data unavailable in 16 patients).

The most commonly used immunosuppression regimen was a combination of cyclosporine A (CyA) with mycophenolate mofetil (MMF) and steroids – 207 patients (42.5%), tacrolimus (TAC) with MMF and steroids – 102 (20.9%) and CyA with azathioprine (AZA) and steroids – 53 patients (10.9%). The mean daily doses of CyA were 5 mg/kg body weight (b.w.), TAC 0.2 mg/kg b.w., MMF 30 mg/kg b.w., and AZA 2 mg/kg b.w. in the first month after transplantation and 3.2 mg/kg b.w., 0.07 mg/kg b.w., 18 mg/kg b.w., and 1.5 mg/kg b.w., respectively, 6 months after the procedure. The doses of CyA and TAC were adjusted based on their whole blood concentrations.

Acute rejection occurred in 85 of the patients (17.5%). In 75 patients of this group (88.2%) as a treatment of this acute rejection, corticosteroid pulses (Solumedrol) were solely used while in 6 patients (7.1%) additionally Muromonab-CD3 (trade name, Orthoclone OKT3) was administered and in 4 anti-thymocyte globulin (ATG) (4.7%) was used.

Patients were informed about the objective of the study and methods of examination, and written informed consent was obtained.

The study was approved by the Bioethics Committee of the Jagiellonian University (No. KBET/100/B/2006).

The mean time from transplant to the first dermatological evaluation was 54.7 ±48.8 months (median 42.5, range 0–298 months).

During the first dermatological evaluation, the whole patient skin was carefully checked for all abnormalities. Dates of birth, transplantation, data about sun exposure, type of immunosuppression therapy, and all complications after the procedure were collected. Viral skin infections were diagnosed based on the clinical examination. Patients were instructed to visit a dermatologist immediately if any of new skin lesions appeared and were followed for the next 5 years. For statistical analysis, the confirmed data from anamnesis and obtained during the evaluation period were used.

Statistical analysis The analysis reported nominal variables indicating the number of patients in the subgroup and the percentage of the relevant group of patients. Frequency tables were analyzed using the χ^2 independence, and in the case of a small number of subgroups (expected number <5), the Fisher's exact test was used.

The χ^2 test was used as a reapeated measure test. Normality of distribution of continuous variables were analyzed using the Shapiro–Wilk test. The variables with normal distribution given the mean ± standard deviation (SD), while for the distributed variables different from the normal median (lower–upper quartile). Differences between the groups were tested by the analysis of variance (3 groups) or Student's *t* test (2 groups) for normally distributed variables and the Mann–Whitney test (2 groups) in the case of distributed variables different from normal.

To study the effect of various factors on the occurrence of diseases in patients after kidney transplantation, a multivariate logistic regression was used. The analysis included those variables that showed a significant association with the occurrence of the disease (in the test of independence the χ^2 test, Mann–Whitney or Student's *t* test), in addition to the described logistic regression models (with a few exceptions, as described in the Results section) entered age, sex, and the time of a kidney transplant since baseline. The results of the logistic regression were shown as odds ratios given for the change of the unit for a variable in the multivariate model with 95% confidence interval.

For the analysis of trends (the relationship of skin disease from the period after kidney transplantation), Kendall's Tau correlation coefficient was used.

Two-sided tests were used. The results were considered statistically significant at $P < 0.05$. A statistical analysis was performed using the Statistica 9.0 software (StatSoft), part of the graph is made using SigmaPlot 8.0 (SPSS inc.).

RESULTS All infectious skin lesions were present in 262 subjects (53.9%). Infectious skin lesions of viral origin were diagnosed in 189 of the 486 studied patients (38.9%). The most frequent lesions were viral warts (38.5%). The mean time from transplantation to the onset of viral infectious skin lesions was 56 months (TABLE 1). The median age of patients with diagnosed viral lesions was 47.9 ±12.7 years (TABLE 2) and the patients with viral skin lesions were older compared with those without lesions 47.6 ±12.7 vs. 45.0 ±13.3 years ($P < 0.033$) (TABLE 3).

The median time from kidney transplantation to dermatological evaluation finding or no

TABLE 1 Number and percentage of patients after kidney transplantation with viral skin lesions and time to their manifestation (months)

Type of changes	Patients after KTx (n = 486)	Time from KTx to lesions appearance
all infectious skin diseases	262 (53.9)	48 (19–88)
viral infections	189 (38.9)	56 (20–96)
warts	187 (38.5)	56 (20–96)
hands	172 (35.4)	56 (20–94)
feet	27 (5.6)	107 (22–163)
other	19 (3.9)	56 (28–69)
herpes zoster	2 (0.4)	121

Data are presented as the median (lower–upper quartile) or as the actual data when changes occurred in less than 3 patients.

Abbreviations: KTx – kidney transplantation

TABLE 2 Age of kidney transplant patients on the diagnosis of infective skin lesions

Type of lesions	Patients after KTx
all infectious skin diseases	48.0 ±12.6
viral infections	47.9 ±12.7
warts	47.9 ±12.7
hands	47.7 ±12.4
feet	53.7 ±12.7
other	46.1 ±15.0
herpes zoster	46 (35; 57)

Data are presented as mean ± standard deviation, given the actual data when the lesion occurred in less than 3 patients

Abbreviations: see TABLE 1

infective viral skin lesions was 53 months, and 37 months, respectively; $P = 0.021$). Analyzing the time from transplantation to the dermatological examination viral warts were diagnosed earlier than herpes zoster. Moreover, viral warts on the hands appeared earlier than those on the feet (TABLE 4).

In the group of postkidney transplant patients, viral skin lesions were present in 43.2% of men and 32.1% of women ($P < 0.014$). The most frequently reported infectious viral lesions were warts: 42.6% of men and 32.1% of women ($P = 0.021$). The warts were mainly localized on the hands (77%; 144/187), feet (4.3%; 16/187), or in other site (face, neck, limbs) (3.7%, 9/187); 15% of the patients had viral warts in more than 1 site (hands and feet, 8.6%; hands and other, 4.8%; 3 and more sites 1.6%). In 2 men (0.7%), herpes zoster was diagnosed (TABLE 5).

The highest number of viral warts was found in the group of patients aged less than 1 year, and more than 10 years after kidney transplantation, 51.9% and 51.7% of the patients, respectively, while between 1–5 and 5–10 years after transplantation, they appeared in 34.3% and 33.7% (TABLE 6).

Analyzing the effect of the immunosuppressive regimen on the occurrence of warts (test of independence, χ^2 test), we demonstrated that (present or past) treatment with CyA ($P = 0.001$) and the current ($P = 0.001$) or past ($P < 0.0001$) AZA were significant factors affecting the occurrence of viral warts. Significantly less frequently, those lesions were observed in patients treated with

TABLE 3 Age distribution in kidney transplant patients with and without infective skin lesions

Types of lesions	Patients with lesions	Patients without lesions	P^a
all infectious skin diseases	47.7 ±12.6	44.0 ±13.4	0.002
viral infections	47.6 ±12.7	45.0 ±13.3	0.033
warts	47.6 ±12.7	45.0 ±13.3	0.031
hands	47.4 ±12.4	45.3 ±13.4	0.091
feet	52.8 ±12.6	45.6 ±13.0	0.005
other	44.5 ±14.5	46.1 ±13.04	0.6
herpes zoster	45.0 ±17.0	46.0 ±13.1	–[b]

a Student's *t* test for unpaired variables, **b** statistical analysis not performed due to 2 patients with herpes zoster

Data are presented as mean ± standard deviation, given the actual data when the lesion occurred in less than 3 patients

TABLE 4 Time from kidney transplantation (months) to dermatological evaluation finding or no infective skin lesions

Types of changes	Patients with lesions	Patients without lesions	P^a (Mann–Whitney test)
all infectious diseases	45 (17–83)	39 (16–82)	0.5
viral infections	53 (18–89)	37 (15–79)	0.021
warts	53 (18–89)	37 (15–79)	0.027
hands	53 (19–89)	38 (15–79)	0.026
feet	80 (19–133)	42 (16–80)	0.007
other	26 (8–60)	43 (17–83)	0.1
herpes zoster	96	42 (16–82)	–

a Student's *t* test for unpaired variables

Data are presented as median (lower–upper quartile), given the actual data when the change occurred in less than 3 patients

TABLE 5 Prevalence of viral skin infections in kidney transplant patients according to sex

Types of lesions	Men (n = 296)	Women (n = 190)	P^a
viral infections,	128 (43.2)	61 (32.1)	0.014
warts, n (%)	126 (42.6)	61 (32.1)	0.021
hands, n (%)	118 (39.9)	54 (28.4)	0.010
feet, n (%)	11 (3.7)	16 (8.4)	0.027
other, n (%)	12 (4.0)	7 (3.7)	0.8
herpes zoster, n (%)	2 (0.7)	0	–

a test of independence, χ^2 (df = 1)

Given the number of patients who experienced changes and interest groups of men or women.

TABLE 6 Viral warts in kidney transplant patients according to the period of time from transplantation to dermatological evaluation

Lesions, n (%)	≤1 year (n = 54)	1–5 years (n = 204)	5–10 years (n = 163)	>10 years (n = 60)
warts	28 (51.9)	70 (34.3)	55 (33.7)	31 (51.7)
hands	25 (46.3)	66 (32.4)	50 (30.7)	28 (46.7)
feet	3 (5.6)	5 (2.5)	8 (4.9)	11 (18.3)
other	2 (3.7)	8 (3.9)	7 (3.7)	1 (1.7)

TABLE 7 Effect of immunosuppressive therapy on the appearance of viral warts

Drug		Viral warts (P^a)
azathioprine	past	<0.0001 (56.3% vs. 29.2%) ↑
	present	0.001 (55.7% vs. 35.6%) ↑
cyclosporine A	past	0.001 (43.8% vs. 28.9%) ↑
	present	0.001 (43.9% vs. 29.3%) ↑
mycophenolate mofetil	past	0.0002 (33.4% vs. 51.5%) ↓
	present	0.004 (34.2% vs. 48.0%) ↓
tacrolimus		<0.0001 (25.9% vs. 44.5%) ↓

a differences in the incidence of disease among those treated vs. untreated with drug was assessed using the χ^2 independence (df = 1); the table shows the level of significance (*P*), and the proportion of patients who developed the disease in the treated vs. the untreated drug

Abbreviations: ↑ – symbol indicates a higher incidence of the disease in patients treated with the drug; ↓ – symbol indicates a lower incidence of the disease in patients treated with the drug

MMF at present (P = 0.004) or in the past (P = 0.0002) and TAC (P = 0.0001) (TABLE 7).

A multivariate logistic regression analysis (including the type of drug used in addition to data such as patient age, sex, time since transplantation, the occurrence of warts before transplantation) showed that only male sex and AZA treatment significantly affected the higher incidence of viral warts, P <0.031 and P <0.007, respectively (TABLE 8).

The study using a multivariate logistic regression analysis showed that the time of immunosuppressive treatment is not a statistically significant factor associated with the presence of viral lesions in patients after transplantation (P = 0.4). It has also been shown that the presence of viral warts prior to transplantation tended to predispose to their appearance after transplantation (P = 0.099).

In patients after kidney transplantation, there was no effect on the occurrence of skin viral lesions of human leukocyte antigen compatibility (P = 0.4), the ABO blood group and Rh factor (P = 0.9), the cause of renal failure (P = 0.3), and the type of treatment (HD or DO) in the past (P = 0.9).

DISCUSSION In kidney transplant patients, the most frequent skin lesions are of viral origin (38.9%) followed by fungal (25.9%) and bacterial (1.2%), which represent 57.4%, 41.0%, and 1.6%, respectively, of all infectious skin complications.[12]

The available literature data provides evidence that infectious skin lesions of viral etiology are the most commonly observed skin complications in patients after organ transplantation.[13,14] In our study, they occurred in 189 patients (38.9%), of which 187 had viral warts, and 2 had herpes zoster. Also in other studies,[14,15] viral warts accounted for the majority of virus detected changes. The available literature indicates that the incidence of viral warts is varied from 11% to 53% of the population of patients after transplantation.[16,17] In our study, its appearance was observed in 38.5% of the patients, which is similar to the results obtained by Ramsay et al. (42%).[17] We observed a correlation between the age of the patients after kidney transplantation, and the presence of viral warts on the feet (patients with warts were much older), and the same observation was made by Pruvost et al.[18]

The number of warts increases with the duration of immunosuppressive therapy, which is consistent with the observations of other authors.[14,18] In the first year after transplantation, this problem affects 11% to 50% of the patients, while after 5 years of the use of immunosuppression it increases up to 95% of organ recipients.[19,20] These changes are caused by the human papilloma virus (HPV), of which the most

TABLE 8 Effect of consecutive risk factors on the appearance of viral warts in kidney transplant patients

Explanatory variable	Odds ratio (95% confidence interval)	*P*
age at baseline, y	1.01 (0.99–1.02)	0.3
male sex	1.61 (1.04–2.47)	0.031
time from kidney transplantation to the start of the study (months)	1.00 (1.00–1.01)	0.4
occurrence of viral warts before kidney transplantation	2.82 (0.82–9.69)	0.099
azathioprine therapy	1.97 (1.20–3.23)	0.007
treatment with cyclosporine A	0.92 (0.40–2.15)	0.9
treatment with mycophenolate mofetil	0.67 (0.41–1.10)	0.12
treatment with tacrolimus	0.60 (0.25–1.45)	0.3

Given the odds ratios and *P* for each explanatory variable in the multivariate logistic regression analysis, the number of visits as a covariate (*P* for the model <0.0001).

commonly isolated HPV types are 1, 2, 3, and 4. The location and appearance of morphological abnormalities usually are no different from that found in patients with normal immunity.[20,21] In transplant patients, more frequently multiple lesions, episodes of relapse,[20] or progression to dysplastic lesions and cancer were observed.[22,23] Spontaneous regression of warts has been rarely observed.[10]

Ramsay et al.[17] found viral warts in 44.3% of the patients 5 years after transplantation, 52.3% of the patients 5–10 years postsurgery, and in 56.9% of the patients over 10 years after transplantation. Similar results were obtained by Pruvost et al.,[18] who at the time of transplantation reported warts in 16% of the patients while 1 year after surgery in 23% of the patients, and after 3, 5, and 7 years after transplantation, 35%, 45%, 54%, respectively. Seckin et al.[14] found viral warts, in as many as 42% of the patients within the first year after kidney transplantation, while Dreno[24] observed its presence in 85% of the patients 5 years after the procedure. In their study, as in other reports, warts were located primarily in the areas exposed to the sun, especially on the hands, were related to sex and occurred more frequently in men (42.6% of men vs. 32.1% of women).[13,21,25]

In our study, the mean time after kidney transplantation to warts appearance was 56 months. The highest number of viral warts was found in the group of patients less than 1 year, and more than 10 years after the transplantation procedure. It may indicate that stronger immunosuppression at the beginning or longer immunosuppressive treatment promote the appearance of warts. We observed as few as 9 patient with recurrent warts after kidney transplantation (1.8% of the group). There was no malignant transformation of warts, and also we did not show, the association between the presence of multiple cutaneous warts (>10), and the risk of skin cancer as described by Ramsay et al.[17] The presence of viral warts on the hands before transplantation predisposed to their appearance after transplantation. This observation may confirm earlier reports indicating that, in cases of viral diseases under the influence of implemented immunosuppressive therapy, there is a reactivation of pre-existing infections. The available literature indicates quite frequent episodes of recurrent warts and cases of progression to dysplastic lesions and squamous cell carcinoma.[20,22,23]

The effect of immunosuppressive drugs on the appearance of skin lesions and the character of warts in patients after transplantation has been the subject of few studies so far. In our study, we have shown that the type of immunosuppressive therapy in the form of "ever or currently used" AZA, and "presently" CyA significantly increased the risk of viral warts. A study by Barba et al.[13] also confirms the promotive effect of AZA, viral warts were in fact more likely in patients treated with prednisolone and AZA, CyA with AZA, and prednisolone than in the group receiving CyA and prednisolone. Other researchers have also observed a much higher incidence of viral warts in patients treated with the immunosuppression regimen containing AZA.[14,25] It has been found that the time of use rather than the dose affected the presence of warts.[25] The incidence of viral skin lesions increases with the time post-transplantation, despite the fact that the doses of AZA are normally lower than those used in the initial phase after transplantation.

Provost et al.[18] noted that patients who after 3 years posttransplantation received less intensive immunosuppression had no viral warts. Effects of a dose may confirm the findings of Barba et al.,[13] according to which the risk of warts was significantly higher with increasing doses of immunosuppressive drugs. While analyzing the results, it should be remembered that for many years, AZA and prednisolone were the main drugs used to prevent rejection of transplanted organs. In our study, the most of kidney transplant patients above 10 years used AZA, which was successfully switched to MMF registered since 1995 for adult patients. Similar changes were observed for calcineurin inhibitors were the percentage of patients receiving CyA steadily decreased while those on TAC increased. Both tendencies cause that patients over 10 years after kidney transplantation were mostly treated with CyA + AZA + steroids, while those below

5 years since transplantation usually received TAC + MMF + steroids. Such treatment policy may have also affected the incidence of warts. The effect of CyA on the incidence of viral warts was also confirmed by other studies.[13] In our study, as in the available literature, there was no effect of HLA mismatch on viral diseases.[13] There was also no effect of the cause of chronic kidney disease and type of dialysis on the occurrence of viral skin changes.

To summarize, we may conclude that the incidence of infectious skin warts in patients after kidney transplantation was dependent on immunosuppression. Analyzing the effect of the type of immunosuppressive therapy on the occurrence of infectious skin lesions, we showed that taking AZA and CyA predisposes to the occurrence of viral warts. A similar relationship between the use of AZA[14,25] and CyA[13] and the occurrence of cutaneous warts have also been reported by other researchers.

In conclusion, the incidence of infectious skin lesions of viral etiology in patients after kidney transplantation is affected by increasing age, male sex, and the length of immunosuppressive therapy. Treatment with CyA and AZA promotes the development of viral warts.

Funding This study was funded by a grant (no KBN/N402 1861 35).

Acknowledgments The manuscript was not published elsewhere except in an abstract form as a poster during 50th ERA-EDTA Congress, Istanbul 2013.

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ARTYKUŁ ORYGINALNY

Skórne infekcje wirusowe u chorych po przeszczepieniu nerki – czynniki ryzyka

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SŁOWA KLUCZOWE

czynniki ryzyka infekcji, immunosupresja, przeszczepienie nerki, skórne infekcje wirusowe

STRESZCZENIE

WPROWADZENIE Infekcyjne zmiany skórne u chorych po przeszczepieniu nerki otrzymujących leczenie immunosupresyjne należą do częstych powikłań.

CELE Celem pracy była ocena częstości występowania oraz analiza czynników wpływających na rozwój infekcyjnych wirusowych zmian skórnych u pacjentów po przeszczepieniu nerki.

PACJENCI I METODY Badaniami objęto 486 chorych, w tym 296 mężczyzn (60,9%) i 190 kobiet (39,1%) w wieku 46,1 ±13,1 lat, po upływie 74,3 ±52,1 miesiąca od przeszczepienia nerki, u których w większości nadal stosowano trójlekową terapię immunosupresyjną. Wszystkie wykryte podczas badania dermatologicznego zmiany skórne szczegółowo opisano, określono ich rodzaj, wielkość, dokładną lokalizację, zależność od wieku, płci i stosowanego leczenia immunosupresyjnego. Następnie pacjentów obserwowano przez 5 lat.

WYNIKI Infekcyjne zmiany skórne o etiologii wirusowej wystąpiły u 189 na 486 badanych chorych (38,9%). Najczęściej występującymi wirusowymi zmianami skórnymi o charakterze infekcyjnym są brodawki (38,5%) i występują one częściej u ludzi starszych (47,6 *vs* 45,0 lat; p <0,033). Brodawki wirusowe obserwowano częściej u chorych płci męskiej (p <0,031). Zmiany wirusowe występowały częściej u chorych leczonych dłużej immunosupresyjnie (53 *vs* 37 miesięcy; p <0,021) oraz otrzymujących azatioprynę i cyklosporynę A (p <0,001). W wieloczynnikowej regresji logistycznej wykazano, że jedynie leczenie azatiopryną istotnie zwiększa ryzyko tych powikłań (p <0,007).

WNIOSKI Na częstość występowania infekcyjnych zmian skórnych u pacjentów po przeszczepieniu nerki otrzymujących leczenie immunosupresyjne mają wpływ starszy wiek, płeć męska i dłuższy czas stosowania immunosupresji. Leczenie cyklosporyną A i azatiopryną sprzyja rozwojowi infekcyjnych brodawek wirusowych.

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Praca wpłynęła: 26.08.2013.
Przyjęta do druku: 25.09.2013.
Publikacja *online*: 26.09.2013.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2013; 123 (12): 686-692