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ORIGINAL ARTICLE

"Acquired epidermodysplasia verruciformis" in kidney transplant patients

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KEYWORDS

Epidermodysplasia verruciformisin;
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Abstract *Background:* Epidermodysplasia verruciformis (EV) is a well known inherited autosomal recessive skin disease associated with numerous early onset viral warts on the sun exposed parts of the body that usually progress into skin malignancies. Kidney transplant patients are also commonly associated with viral warts that might change into skin cancers.

Objective: To describe the clinical pictures of extensive viral warts with skin malignancies in kidney transplant patients in comparison with inherited (EV) features.

Patients and methods: This case controlled study that included 130 patients with kidney transplantation was done in kidney transplantation centers in Baghdad and Al-Karma Teaching Hospitals during December 2002 to September 2004. All recruited patients were receiving multiple immunosuppressive drugs like methyl prednisolone succinate, oral prednisolone, azathioprine and cyclosporine. History was taken from all patients including all the relevant points. These patients were divided into three groups according to the duration of kidney transplant: *group A* 1–10 years, *group B* 11–20 years and *group C* more than 20 years. Biopsies were performed from the viral warts lesions and the associated tumors.

Two hundred and sixty apparently healthy individuals, 206 males and 54 females had been examined as control cases for the presence of viral warts and tumors. These control cases had been taken randomly from general population in multiple regions in Baghdad.

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Results: Sixty-five patients out of 130 with kidney transplantation had viral warts. Their ages ranged from 20 to 71 (45.49 ± SD 10.82) years, 51 males and 14 females, while the duration of the warts ranged from 0.5 to 10 (3.74 ± SD 2.67) years. The distribution of patients with viral warts among the groups was as follows: *group A* 28 (43.1%), *group B* 30 (46.2%) and *group C* 7 (10.7%) cases. Viral warts were seen in 10 (3.8%) of the control group. There were statistically significant differences between patients and control cases (P value < 0.001). Most of the viral warts in patients with kidney transplantation were multiple and of the verrucae vulgaris type. They were mainly located on the exposed areas of the body, mostly on the face and dorsa of hands.

Skin malignancies were observed in 6 (9.2%) cases: five squamous cell carcinomas and one case of basal cell carcinoma. Squamous cell carcinoma was mainly located on the lower lips in 3 cases and 2 on the dorsa of hands, while basal cell carcinoma was observed on the nose. Two cases (7.1%) of squamous cell carcinoma were seen in *group A*, 2 (6.6%) in *group B* and 1 (14%) in *group C*. One case of basal cell carcinoma was noted in *group B* .No skin malignancy was observed in the control group.

Conclusion: Kidney transplant patients have an increased susceptibility to infection with human papilloma virus and have served as a model for viral induced carcinogenesis. This collection of features deserves the term "acquired epidermodysplasia verruciformis".

1. Introduction

Epidermodysplasia verruciformis (EV) is an inherited autosomal recessive gene disorder in which there is early onset, numerous, widespread, persistent, and refractory infection with human papilloma virus (HPV) (Sterling and Kurtz, 1998; Penneys, 1997; Lowy et al., 2003; Odom et al., 2000).

The individual lesions typically have either the appearance of warts or flat scaly red–brown macules, resemble lesions of pityriasis versicolor or pityriasis rosea .The first type of lesion is usually caused by the same HPV types as those found in flat warts in the general population (e.g HPV-3 and 10), while the second one is usually caused by EV HPV types (e.g HPV-5, 8, 9, 12, 14, 15, 17, 19–25, 28, 29, 36–38, 47, 49, 50) (Penneys, 1997; Lowy et al., 2003; Odom et al., 2000; Ostrow et al., 1987; Pfister, 1987; Yutsudo et al., 1994). There may be more then one HPV type in the same patient (Ostrow et al., 1987; Pfister, 1987).

The pathogenesis of this syndrome is unknown but is felt to be a specific defect of cell mediated immunity (Penneys, 1997; Lowy et al., 2003; Odom et al., 2000; Majewski et al., 1986).

Some EV patients are at high risk of developing cutaneous squamous cell carcinoma (Sterling and Kurtz, 1998; Penneys, 1997; Lowy et al., 2003; Odom et al., 2000; Orth, 1986). Although, pityriasis like lesions caused by any EV type may be at increased risk of becoming malignant, the risk appears to be greatest for those caused by HPV-5, 8 and 47 types (Sterling and Kurtz, 1998; Penneys, 1997; Lowy et al., 2003; Odom et al., 2000; Pfister, 1987; Orth, 1986).

The lesions of individuals with EV who have only flat warts caused by non-EV HPV types do not seem to be at increased risk of becoming malignant. Squamous cell carcinomas develop in 30–60% patients. Most often, skin cancers appear on sun–exposed surfaces, but they can appear on any part of the body. They begin to appear at ages 20–40. HPV-5, 8 and 47 are found in more than 90% of EV skin cancers. The squamous cell carcinoma may appear denovo but usually appear on the background of numerous actinic keratosis and lesions of Bowen's disease, locally and usually aggressive (Sterling and Kurtz, 1998; Penneys, 1997; Lowy et al., 2003; Odom et al., 2000; Sharquie et al., 2007).

There is a high rate of registering records in the last two decades of cases with clinical features almost similar to inherited EV. These cases were exclusively kidney transplant patients with immunosuppressive drugs. This case controlled study was designed to describe the clinical pictures of extensive viral warts with skin malignancies in kidney transplant patients in comparison with inherited EV features.

2. Patients and methods

This case controlled study that included 130 patients (103 males and 27 females) with kidney transplantation was carried out in kidney transplantation centers in Baghdad and Al-Karma Teaching Hospitals, from December 2002 to September 2004. All recruited patients were receiving the immunosuppressive drugs after renal transplantation. They consisted of rapidly decreasing doses of intravenous methylprednisolone succinate for the first 3 days followed by oral prednisolone, tapered slowly to a maintenance dose of 10 mg/day or 20 mg every other day by the end of the first year. Azathioprine was given at doses ranging form 1 to 4 mg/kg/day according to the white blood cell count. Cyclosporine, in combination with azathioprine was given orally starting with 8–10 mg/kg/day, decreased every 2 weeks by 2 mg/kg/day to a maintained dose of 5 mg/kg/day. History was taken from all patients including age, sex and date of transplantation.

These patients were divided into three groups according to the duration of kidney transplant: *group A* 1–10 years, *group B* 11–20 years and *group C* more than 20 years. Biopsies were performed from the viral warts lesions and the associated tumors.

Two hundred and sixty apparently healthy individuals, 206 males and 54 females had been examined as the control group for the presence of viral warts and tumors. These control cases had recruited randomly from the general population in multiple regions in Baghdad.

3. Results

Sixty-five patients (50%) out of 130 patients with kidney transplantation had viral warts. The ages of these patients ranged

Table 1 Showing the demographic features of 65 (50%) patients out of 130 patients with kidney transplantation associated viral warts.

Groups	Duration of kidney transplant	Mean ages of patients	No. of patient with viral warts	Location of viral warts	BCC and location	SCC and location
Group A	1–10 years	45.49 ± SD 10.82 years	28 (43.1%)	Face and dorsa of hands	Nil	Two (7.1%) lower lip, dorsum of hand
Group B	11–20 years	45.49 ± SD 10.82 years	30 (46.2%)	Face and dorsa of hands	One nose	Two (6.6%) lower lip, dorsum of hand
Group C	More than 20 years	45.49 ± SD 10.82 years	7 (10.7%)	Face and dorsa of hands	Nil	One (14%) lower lip

from 20 to 71 years with a mean of 45.49 ± SD 10.82 years. There were 51 males and 14 females with a male/female ratio 3.64:1. The duration of the warts ranged from 0.5 to 10 years with a mean of 3.74 ± SD 2.67 years.

The distribution of patients with viral warts among the groups was as follows: *group A* 28 (43.1%), *group B* 30 (46.2%) and *group C* 7 (10.7%) cases. So, 37 (57%) cases of viral warts occurred after 11 years of kidney transplantation, while, viral warts were seen in 10 (3.8%) individuals in the control group. There was statistically significant difference between patients and control cases (P value < 0.001).

Most of the viral warts were multiple and of the verrucae vulgaris type.

Skin malignancies were observed in 6 (9.2%) cases of kidney transplantation: 5 cases of squamous cell carcinoma and one case of basal cell carcinoma. Squamous cell carcinomas were mainly located on the lower lips in 3 cases and 2 on the dorsa of hands, while basal cell carcinoma was observed on the nose. Two cases (7.1%) of squamous cell carcinoma were seen in *group A*, 2 (6.6%) in *group B* and 1 (14%) in *group C*. One case of basal cell carcinoma was noted in *group B*. No skin malignancies were observed in the control individuals. Biopsies and histopathological examination of the viral and skin tumors confirmed the diagnosis (Table 1).

4. Discussion

Kidney transplant patients often have immunosuppression as a result of the multiple immunosuppressive drugs that are used to prevent organ rejections (Hamilton, 1988; Rowan et al., 1988). This immunosuppression usually ends with increased tendency for infections especially viral warts (Rowan et al., 1988).

In the present work, viral warts had been observed in 50% of kidney transplant patients in the first 10 years of transplantation, while it had been recorded in 90% within the first 5 years of transplantation in other countries (Odom et al., 2000; Rowan et al., 1988; Rudlinger et al., 1986; Leigh and Glover, 1995a,b). So in Iraq, patients with kidney transplantations had a tendency to develop late onset viral warts when compared with other countries, as 50% of patients with kidney transplantations had their viral warts after 11 years of their kidney transplant. Skin malignancies mainly squamous cell carcinoma and basal cell carcinoma were seen in 6 (9.2%) cases of kidney transplant patients with viral warts. In all cases, these lesions were observed on the sun exposed areas mainly the face. The increase in the rate of malignancies among patients with kidney transplantations was similar to what has been published (Odom et al., 2000; Rudlinger et al., 1986; Leigh and Glover, 1995a; Sharquie and Al-Sadawi, 2001).

Inherited EV is usually an autosomal recessive disease, that is associated with early onset of numerous viral warts similar to pigmented pityriasis rosea or tinea versicolor like lesions (Sterling and Kurtz, 1998; Penneys, 1997; Lowy et al., 2003; Odom et al., 2000) with a high tendency to develop skin malignancies especially squamous cell carcinoma in 30–60% of cases. They begin to appear at ages 20–40 years (Odom et al., 2000; Sharquie et al., 2007). Most of the malignant tumors remain local, but regional and distant metastasis may occur (Sterling and Kurtz, 1998; Penneys, 1997; Lowy et al., 2003). The serotypes of HPV that responsible for this oncogensity are 5, 8 and 47 types (Sterling and Kurtz, 1998; Penneys, 1997; Lowy et al., 2003; Odom et al., 2000; Pfister, 1987; Orth, 1986). In Iraq, there is a focus of inherited EV as a result of inter-consanguineous marriages. These cases are usually seen in Sammaraa City (100 km North of Baghdad) (Sharquie et al., 2007; Al-Hamami et al., 1986). The morphology of the rash is similar to that what had been published, present in early childhood with pigmented pityriasis rosea or tinea versicolor like lesions on the sun exposed parts of the body (Sterling and Kurtz, 1998; Penneys, 1997; Lowy et al., 2003; Odom et al., 2000; Sharquie et al., 2007).

They are usually associated with skin malignancy but in Iraqi cases, these tumors are usually were aggressive and had a high tendency to regional metastasis as we observed (Sharquie et al., 2007). Squamous cell carcinoma arising from per-orbital viral warts that lead to orbital invasion and eye inoculation (Sharquie et al., 2007).

It is well known that EV associated with skin malignancies like squamous cell carcinoma and basal cell carcinoma and HPV types 5, 8 and 47 have been incriminated in their etiopathogenesis (Sterling and Kurtz, 1998; Penneys, 1997; Lowy et al., 2003; Odom et al., 2000; Pfister, 1987; Orth, 1986). Most recently, it has been observed that HPV had contributed in the development of squamous cell carcinoma even in patients without viral warts (Kazutoshi et al., 2004; De-Jong Tieben et al., 1995). So, HPV in patients with kidney transplant could act as a co-factor in the tumor development along with immunosuppression, solar radiation and other environmental factors (Sterling and Kurtz, 1998; Penneys, 1997; Lowy et al., 2003; Odom et al., 2000; Leigh and Glover, 1995b).

In reviewing, the clinical picture of the inherited EV in comparison with that of the clinical features in patients with kidney transplant, we found the following similar observations in both conditions: there is immunosuppression because of impaired cell mediated immunity, the rash occurs in young patients,

there are numerous skin lesions, they are recalcitrant to therapy, viral warts and skin cancers occur on any part of the body especially in sun exposed areas of the body and skin malignancies are a common feature (Sterling and Kurtz, 1998; Penneys, 1997; Lowy et al., 2003; Odom et al., 2000; Ostrow et al., 1987; Pfister, 1987; Yutsudo et al., 1994; Majewski et al., 1986; Orth, 1986; Hamilton, 1988; Sharquie and Al-Sadawi, 2001; De-Jong Tieben et al., 1995; Annelies et al., 2002; Jeffrey et al., 2000; Shamanin et al., 1994).

So, the infective agent, the immune defect, clinical pictures of the skin rash and the course of the disease in kidney transplant patients having many similarities with that of the inherited form of EV (Leigh and Glover, 1995a,b; Sharquie and Al-Sadawi, 2001; Kazutoshi et al., 2004; De-Jong Tieben et al., 1995; Annelies et al., 2002; Jeffrey et al., 2000; Shamanin et al., 1994). Accordingly, we think that the clinical features in patients with kidney transplant deserve the term acquired epidermodysplasia verruciformis.

In conclusion, patients with kidney transplantation had a high frequency of viral warts and skin malignancy in the exposed parts of the body and these might simulate EV.

Also, we describe a disease in kidney transplants patients that have many similarities with inherited type of EV that deserve the term acquired epidermodysplasia verruciformis form.

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