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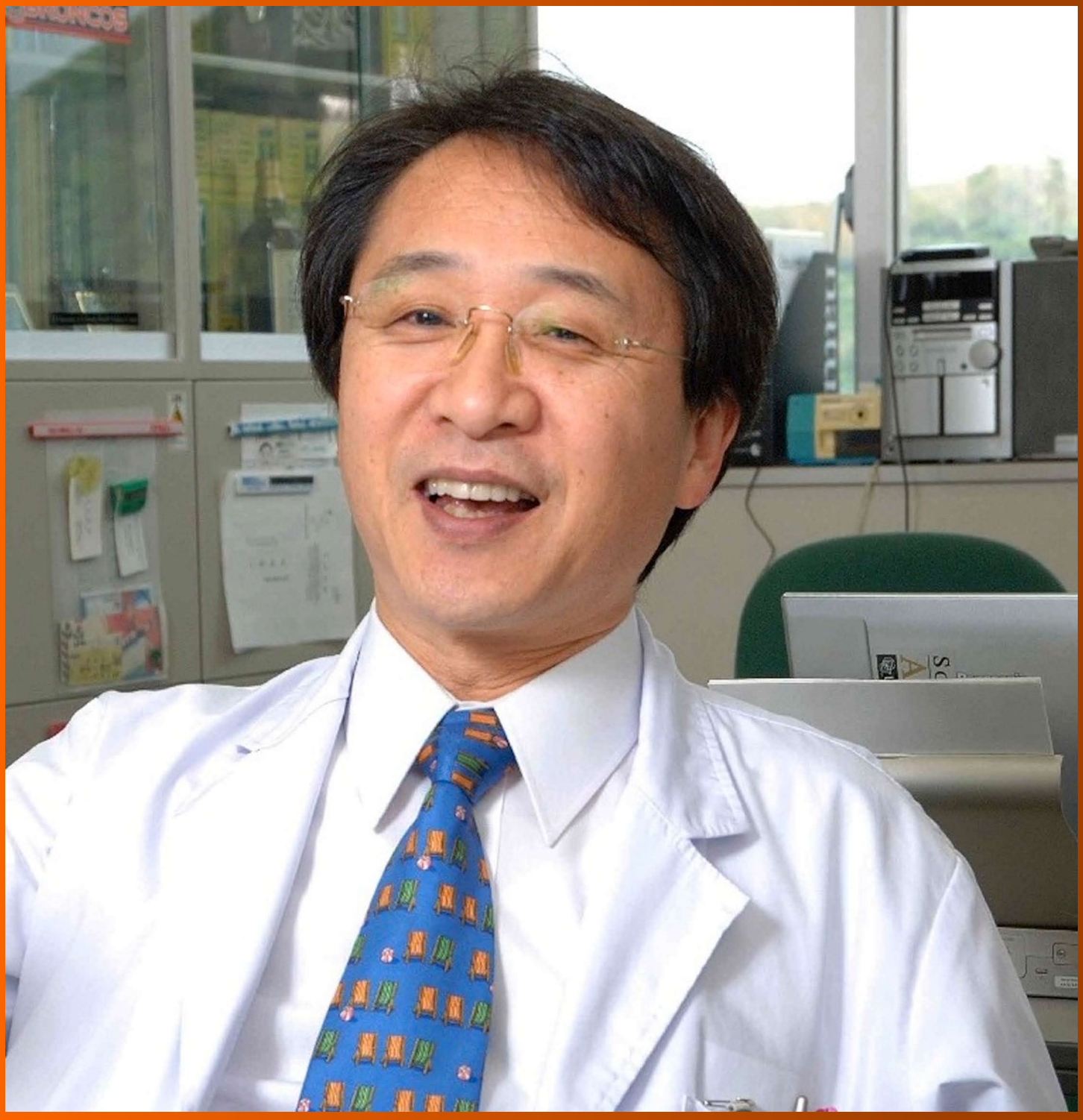

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ORIGINAL ARTICLE

Observational Study

Multi-channeling optimized radiofrequency energy: A new age in well-established radiofrequency technology

Cruzy Tagger, Inna Belenky

Cruzy Tagger, Inna Belenky, Viora Inc., Jersey City, NJ 07306, United States

Author contributions: Tagger C and Belenky I contributed equally to this work.

Institutional review board statement: The study performed according good clinical practice requirement.

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: Both authors, both authors are employees in Viora Company that manufactures the RF system used in the study. However, both authors did not receive any additional financial or other benefit/interest due to this study or publication. All data provided in the study is original and not modified.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at inna@vioramed.com. Participants gave informed consent for data sharing.

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Abstract

AIM

To evaluate the safety and efficacy of Viora's new multi-polar radiofrequency (RF) handpiece.

METHODS

A group of twelve volunteers (11 females and 1 male) participated in the current study, ranging in age from 23-70 years with Fitzpatrick skin type Ⅱ-Ⅴ. The inclusion criteria for the enrollment were no contraindications for the treatment, body mass index (BMI) < 35 and local fat accumulation or cellulite formation. A total of 19 treatment areas were treated in the study: 9 abdomen, 2 abdomen plus flanks, 2 arms and 6 thighs. The treatment performed with new multi-polar RF handpiece (V-FORM) with 4 levels of RF power (up to 50 W), 4 levels of vacuum pressure intensity (up to 500 mbar) and 4 operational modes (0.8, 1.7 and 2.45 MHz). Circumferential reduction and cellulite reduction treatments were performed once a week (7 ± 1 d) for a treatment series of 3-8 sessions. The clinical assessment of the treatment outcomes included skin moisture level, skin impedance, body temperature, circumferential measurements, clinical photographic assessment and BMI.

RESULTS

Ten of twelve patients completed the treatment course. No side effects were recorded during the study. The skin responded with slight erythema and sometimes edema, which is considered a positive end-point. All patients maintained a stable weight during the

entire period of the study. No patient underwent any treatments or took medications for fat volume reduction during the study. A moderate positive correlation was found between the patient's age and BMI (correlation coefficient 0.54). The initial body temperature increased in average to 34.0 ℃ from 31.9 ℃, the initial skin moisture level increased to an average 40.98% from 38.9% and the initial skin impedance decreased by 3.8%-35.9% by the end of the treatment course. The pre-heating time for all body areas ranged between 1-6 min with negative correlation to the body's end-point temperature (correlation coefficient -0.31). All patients responded to the treatment and showed some degree of circumferential reduction (up to 15 cm), on at least one of two-three measured points.

CONCLUSION

According to clinical data collected in this study, the new V-FORM handpiece represents an effective treatment with 100% response rate, with the safest treatment profile.

Key words: Radiofrequency; Vacuum; Body contouring; Circumferential reduction; Cellulite

Core tip: The significant change in circumferential measurements post-V-FORM treatments can be contributed not only to volume reduction due to improved metabolic rate and enhanced natural lipolysis, but also to edema reduction due to vacuum pressure integrated in the handpiece. Moreover, this technology enables the control of radiofrequency depth penetration which allows finishing the treatments with a skin tightening effect using higher radiofrequency frequencies (1.7 and 2.45 MHz).

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INTRODUCTION

Local fat accumulation and cellulite formulation are two main symptoms related to the reduced metabolic rate in the tissue and rigid connective tissue. Non-invasive procedures based on different modalities such as high intensity focused ultrasound energy (HIFU), radiofrequency (RF), infrared light (IR), cryolipolysis, low-level laser therapy (LLLT), cavitation ultrasound, *etc.*[1-9], in their principle indicated to induce natural lipolysis and reduce fat volume. Technologies that aimed to heat the adipose tissue mainly focused on improving the blood microcirculation to improve the metabolic rate in the impact tissue. In several RF-based systems the thermal heat is combined with vacuum to produce mechanical pressure[3-7,10]. The addition of mechanical pressure enhances the improvement of blood microcirculation and stimulates lymphatic drainage.

The distribution of RF's electrical current mainly depends on the geometry of the device's electrodes. In the esthetic market, two typical configurations are used: Monopolar and bipolar. The major difference between these two configurations is in the way the RF current is controlled and directed at the target tissue[11]. The main advantage of a bipolar configuration is the controlled distribution of RF current inside the tissue, which is limited by distance between the two electrodes. Recently in the esthetic market new terms have sprouted up, such as multi-polar, tri-polar, octi-polar, *etc*. In this concept, the multi-polar RF is an engineering modification of a bi-polar configuration, where more than one pair of bi-polar electrodes exists in the handpiece[10]. The main advantage of a multi-polar handpiece is the ability to cover a much larger treatment area in one pulse, which in most cases leads to faster heating of the treated tissue and its ability to deliver homogeneous distribution of the heat.

The aim of this clinical study was to evaluate the safety and efficacy of Viora's new multi-polar RF handpiece (V-FORM) based on channeling optimized RF energy (CORE), Viora's proprietary technology[10].

MATERIALS AND METHODS

Case study group

A group of twelve volunteers (11 females and 1 male) participated in the current study, ranging in age from 23-70 years (average 43.7, SD ± 14.1) with Fitzpatrick skin type Ⅱ-Ⅴ. The inclusion criteria for the enrollment were no contraindications for RF treatment, body mass index (BMI) < 35 and local fat accumulation or cellulite formation. A total of 19 treatment areas were treated in the study: 9 abdomen, 2 abdomen plus flanks, 2 arms and 6 thighs (Table 1).

The initial body weight range of the patients was 57.3-78.7 kg (average 67.64, SD ± 7.56) with a height range between 150-180 cm (average 163.8 cm, SD ± 7.88) and a calculated BMI of 22-31 kg/m^2 (average 25.4, SD ± 2.2). Six patients were in the range of normal "healthy weight" (BMI 18.5-25 kg/m^2), five patients were in the "overweight" category (BMI 25-30 kg/m^2) and one patient was in the "obese class I" (moderately obese) category (BMI 30-35 kg/m^2) (Table 1).

Handpiece description

The new multi-polar RF handpiece (V-FORM) utilizes Viora's proprietary CORE technology with vacuum[10], which represents the Multi-CORE technology. V-FORM handpiece has 4 levels of RF power (up to 50W), 4 levels of vacuum pressure intensity (up to 500 mbar) and 4 operational modes (Mode Ⅰ-Ⅳ) with three RF frequencies: 0.8, 1.7 and 2.45 MHz and additional

Table 1 Case study patient details

Patient ID	Treatment area	Age	BMI	Number of treatments
VF-001	Thighs, abdomen plus flanks	28	23	6
VF-002	Abdomen	33	22	7
VF-003	Abdomen	44	26	6
VF-004	Abdomen	56	26	8
VF-005	Abdomen	31	26	Dropped from the study
VF-006	Abdomen	40	26	3
VF-007	Abdomen and thighs	23	25	Dropped from the study
VF-008	Arms and abdomen	70	31	8
VF-009	Thighs	34	25	3
VF-010	Abdomen plus flanks	61	27	5
VF-011	Abdomen	47	24	2
VF-012	Thighs	57	23	3
Average		43.7	25.4	5.1
SD (±)		14.1	2.2	2.1

BMI: Body mass index.

operation mode which includes all three RF frequencies. The V-FORM handpiece incorporates integrated IR thermometer, continuous impedance measurement system and interchangeable applicators in different sizes.

Treatment regimen

Circumferential reduction and cellulite reduction treatments were performed once a week (7 ± 1 d) for a treatment series of 3-8 sessions. Each treatment area was treated for 15-20 min, according to the treatment area's size. The treatments were performed according to Viora's standard protocol.

Clinical assessment

The clinical assessment of the treatment outcomes included several measurements and tools: The skin moisture level measured with a digital moisture monitor (Skin Testing Checker, Hautpflege-Konzepte aus Erfahrung) before the treatment and immediately post treatment. The measurement was performed on the same spot of the body, after the glycerin was applied. According to the digital moisture monitor indicator, values < 30% indicate extremely dehydrated skin, values between 31%-36% indicate dehydrated skin, values of 34%-47% indicated normal skin and values > 48% indicated excellent hydration; a skin impedance measurement was conducted according to Ohm's law, in which the impedance was derived from the peak voltage detected during the "test pulse" of the V-FORM handpiece after the electrodes came in touch with the skin. This measurement was performed in a separate test, on 10 randomly chosen treatment areas before the treatment and immediately post treatment on the same spot of the body, after the glycerin is applied; body temperature was measured *via* an integrated IR thermometer, at three times points: Before, during and immediately post treatment; circumferential measurements were performed using the same tape measure tool at the same points on the treated area. Two-three measurement points with 5 cm distance in between were taken for each treatment area at three times: before, middle of course and four weeks after the last treatment. The circumferential change (in cm) was calculated as the following: Circumference (cm) recorded in the baseline meeting, minus circumference (cm) recorded four weeks after the last session; BMI was calculated according to standard guidelines, where weight in kg (kilograms) is divided by height in square meter. The body height and weight were measured according to a standardized protocol where patients are requested to stand without shoes and heavy outer garments for the measurement[12]. The calculation of BMI conducted during the enrollment meeting and four weeks after the last treatment; clinical photographic assessments were recorded twice: (1) during enrollment meeting-(before the first treatment); and (2) four weeks after the last treatment; finally, the treating personnel were asked to record and immediately report any adverse event or unexpected side-effect.

Statistical analysis

For statistical analysis all tests were performed using Microsoft Excel 2010. In total, ten patients were included in the statistical analysis since two patients didn't complete the treatment course. Descriptive analysis was performed on the treated group and the number of valid cases for each test, minimum and maximum values, mean and standard deviation (SD), correlations between two values (CORREL) and percentage were calculated.

RESULTS

Ten of twelve patients completed the treatment course. No side effects were recorded during the study. The skin responded with slight erythema and sometimes edema, which is considered a positive end-point.

All patients maintained a stable weight (weight fluctuations were limited to -0.4 and + 0.6 kg) during the entire period of the study. No patient underwent any treatments or took medications for fat volume reduction during the study.

A moderate positive correlation was found between the patient's age and BMI (correlation coefficient 0.54).

The pre-heating time for all body areas ranged between 1-6 min (average 2.26 min) with a low negative correlation to the body's end-point temperature (correlation coefficient -0.31).

The initial body temperature (temperature before the treatment) ranged between 31 ℃-35 ℃ as the baseline (average 31.9 ℃) and increased to 32 ℃-36 ℃ (average 34.0 ℃) by the end of the treatment course.

The initial skin moisture level (detected before the treatment) ranged between 28.5%-49.0% as the baseline (average 38.9%) and increased to 31%-50% (average 40.98%) by the end of the treatment course (these values are not related to the skin impedance test described in Table 2). The skin moisture level measured at the end of each treatment ranged between 28.6%-65.0% (average 47.2%) which represents a 0.4%-31.4% change in the

Table 2 Skin impedance change post treatment (correlated to skin moisture level)

Patient ID	Treatment area	Skin moisture level (%)			Impedance (Ω)		
		Initial	End	Change (%)	Initial	End	Change (%)
VF-001	Abdomen	38.9	48.4	20	156.4	123.5	21.0
VF-002	Abdomen	32.0	54.2	41	201.9	188.0	6.9
VF-003	Abdomen	39.6	46.1	14	139.1	114.6	17.6
VF-004	Abdomen	38.5	46.7	18	147.7	94.6	35.9
VF-005	Abdomen	38.9	48.4	20	143.9	97.0	32.6
VF-006	Abdomen	41.6	48.3	14	144.0	132.0	8.3
VF-007	Abdomen	38.9	48.4	20	144.2	104.2	27.7
VF-008	Abdomen	36.3	47.0	23	104.8	95.7	8.6
VF-009	Thigh	37.2	46.6	20	216.5	179.3	17.2
VF-010	Abdomen	40.0	56.3	29	114.3	110.0	3.8
Average		38.2	49.0	21.7	151.3	123.9	18.0
SD (±)		2.5	3.2	7.6	32.7	32.1	10.7

Table 3 All measurement points of circumferential reduction per treatment area, number of treatments and body mass index (each line represents a separate measurement point)

Area	Circumference measurement		Circumferential reduction (cm)	Circumferential reduction (%)	Number of treatments	BMI (kg/m^2)
	Baseline (cm)	4 wk post last treatment (cm)				
Thighs	63	62.5	0.5	0.8	6	23
	58	58	0	0		
	64	63.5	0.5	0.8		
	56	56	0	0		
	56.7	54.2	2.5	4.6	3	25
	52.5	51.4	1.1	2.1		
	40.4	39	1.4	3.6	3	23
	40	39.4	0.6	1.5		
Abdomen	94	90	4	4.4	6	23
	71.5	71	0.5	0.7		
	92	90	2	2.2	4	27
	96	94	2	2.1		
	87	85	2	2.4		
	92	90.5	1.5	1.7	6	26
	93	95	-2	-2.1		
	87	86.5	0.5	0.6		
	83	82	1	1.2	8	26
	91	87	4	4.6		
	101	95	6	6.3		
	112	100	12	12	5	31
	104	104	0	0		
	112	97	15	15.5	8	31
	104	96	8	8.3		
	92	89	3	3.4	5	27
	96	92.5	3.5	3.8		
	87	84	3	3.6		
Arms	38	37	1	2.7	4	31
	36	34	2	5.9		
	38	35	3	8.6	8	31
	36	38	-2	-5.3		
	35	34	1	2.9	4	31
	35	36	-1	-2.8		
	35	33.2	1.8	5.4	8	31
	35	34	1	2.9		

BMI: Body mass index.

moisture level post-treatment (average 9.23% change).

A test that aimed to evaluate the change in skin impedance was performed separately on ten randomly chosen treatment areas (Table 2). The initial skin impedance (detected before treatment) ranged between 104.8-216.5 Ω in the baseline (average 151.3 Ω, SD ± 32.7) and decreased by 3.8%-35.9% (average 18%) by the end of the treatment, which represents a 4.4-53.1 Ω change in the impedance post-treatment.

A moderate negative correlation was found between

the changes in the skin's moisture level and skin impedance (correlation coefficient -0.5) with similar coefficient between initial values of impedance and skin moisture level (Table 2). This founding was expected, since blood and parts of the body with high water concentration have lower electrical resistance[10].

All patients (10 of 10) responded to the treatment and showed some degree of circumferential reduction, on at least one of two-three measured points. The measured circumferential reduction of all 36 measurement points ranged from -2 cm (gained circumference) to 15 cm, with an average reduction of 2.78 cm (SD ± 3.38) (Table 3). From a total 36 measurement points, only three measurement points did not show any change in the circumference, (0 cm) and three showed an increase in circumference (negative values in Table 3). Thighs showed the lowest percentage of circumferential reduction (1.68%), followed by the abdomen (4.28%) and arms (4.74%). A negligible positive correlation was found between the percentage of circumferential reduction and number of treatments (correlation coefficient 0.21). However, a low positive correlation was found between a percentage of circumferential reduction and BMI (correlation coefficient 0.44).

DISCUSSION

In this study, 100 percent of patients responded to the V-FORM treatment with at least a 0.6% circumferential reduction on one of the measurement points, indicating that RF treatment has influence on all types of patients. No correlation between the circumferential reduction and the number of treatments (correlation coefficient 0.21) may indicate that treatment response is based on individual characteristics of the patient such as metabolic rate, age and BMI. The positive correlation between circumferential reduction and BMI (correlation coefficient 0.44) supports this conclusion. Interestingly, the high BMI values (above 30 kg/m^2) were mostly considered as exclusion criteria for RF-based treatments. In this study, the positive value of correlation between circumferential reduction and BMI indicates that the higher the patient's initial BMI, the higher percentage of circumference reduction we can achieve. Moreover, the patient with the highest BMI in this study (BMI 31 kg/m^2) was also the most responsive to the treatment, with the highest circumferential measurement values and percentages (15.5% and 8.3%, Figure 1). These findings may suggest the multi-polar RF together with CORE technology may represent a non-invasive solution for high BMI patients. However, in order to establish a more accurate recommendation, additional study with a bigger cohort size, with BMI 30-35 needs to be conducted. The moderate positive correlation between the patient's age and BMI was also expected due to the fact that the metabolic rate of the body reduces with age, which leads to higher values of BMI. The positive correlation between age and BMI was also showed in several unrelated studies[13,14].

Since in this study, all patients had maintained a stable weight, the circumferential reduction can by directly related to the treatment itself. Contrary to fat destruction techniques, such laser lipolysis, liposuction, cavitation ultrasound, *etc*., the RF-based treatment aimed to increase the metabolic rate and enhance natural lipolysis of the fat cells without hypodermal distraction[10]. The assessment of improvement in blood circulation can be evaluated *via* the changes in initial body temperature, skin moisture level and skin's impedance. In this study, the increase in initial body temperature from an average of 31.9 ℃ to an average of 34.0 ℃ by the end of the treatment course indicates improvement in the local blood microcirculation. This data is further supported by an increase in the initial skin moisture level (from an average of 38.9%-40.98%) and even more by an 18% change in the skin impedance. The negative correlation between skin moisture level and skin impedance (correlation coefficient -0.5) indicates that low water concentration contributes to the skin resistance as showed by high values of impedance. This finding is expected, since blood, and parts of the body with high blood content, have the highest electrical conductivity. The 0.4%-31.4% change (average 9.23%) in the moisture level post-treatment is additional supporting point to prove improved blood circulation. The change in the skin's moisture level at the end of the treatment course compared to the initial level recorded in the first treatment (average change of 40.98%) indicates a long term influence on the extracellular matrix achieved *via* fibroblast stimulation. This finding stands together with previously published data on the influence of RF and, in particular, CORE technology, on the dermal tissue[10].

In addition, the significant change in circumferential measurements post-V-FORM treatments can be contributed not only to fat volume reduction due to improved metabolic rate and enhanced natural lipolysis, but also to edema reduction due to vacuum pressure integrated in the handpiece. Moreover, the Multi-CORE technology enables the control of RF depth penetration which allows finishing the treatments with a skin tightening effect using higher RF frequencies, at 1.7 and 2.45 MHz.

Thighs showed the lowest percentage of circumferential reduction with only 1.68% (compared to abdomen and arms with 4.28% and 4.74%, respectively). This can be explained by the fact that patients who participated in the study for thigh treatments exhibited cellulite appearance and not local fat accumulation (Figure 2).

The design of the V-FORM handpiece includes multiple electrodes (multi-polar RF) enables the coverage of big treatment areas in a very short time (the time needed to increase the body temperature to 39 ℃-42 ℃ measured an average 2.26 min pre-heating time). The negative correlation between pre-heating time and the body's end-point temperature related to the fact that patients with higher skin conductivity can be heated much faster and to higher end-point temperatures.

During the entire study no adverse effects were recorded. This can be attributed to the fact that the

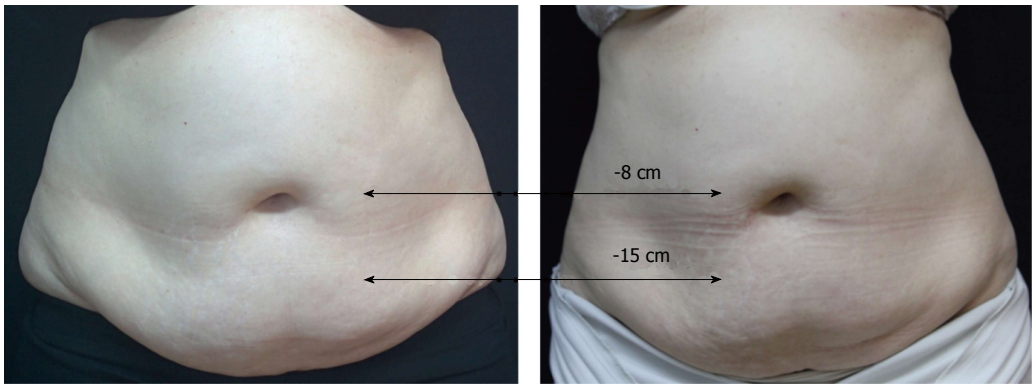

Figure 1 A 70-year-old female (body mass index 31) before and 4 wk after 8 treatment sessions (after), with 15 cm and 8 cm circumferential reduction (according to 2 measurement abdomen points).

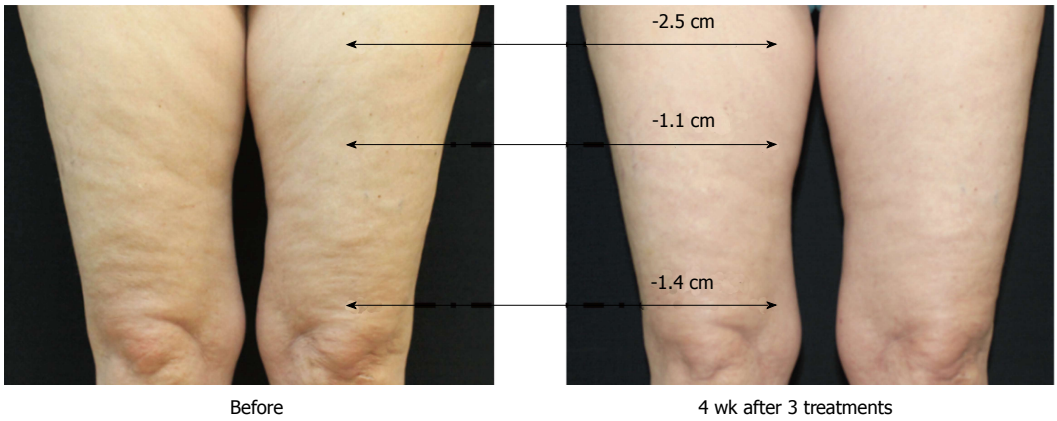

Figure 2 A 57-year-old female (body mass index 31) before and 4 wk after 3 treatment sessions with 2.5 cm, 1.1 cm and 1.4 cm circumferential reduction (according to 3 measurement points). Reduction of cellulite grade 3 to grade 2.

V-FORM handpiece monitors the skin impedance during the entire pulse and controls the RF energy current release accordingly. The design of the applicator itself contributes to an even vacuum spread over the tissue which dramatically reduces the chance to cause hematomas. Multiple electrodes contribute to the homogeneous heat spread over the tissue without hot-spots, which increase patients' tolerance to the treatments and also reduces the appearance of side effects. In addition, as expected, all skin types (Ⅰ-Ⅴ) that were included in the study reacted to the treatment regardless of the skin phototypes, as RF energy has similar behavior in all Fitzpatrick skin types.

In conclusion, according to clinical data collected in this study, the new V-FORM handpiece represents without any doubt an effective treatment with 100% response rate, with the safest treatment profile.

COMMENTS

Background

Local fat accumulation and cellulite formulation are two main symptoms related to the reduced metabolic rate in the tissue and rigid connective tissue. Invasive fat removal procedures are usually too expensive, with long downtime and complication. Therefore non-invasive procedure commonly used. Technologies that aimed to heat the adipose tissue mainly focused on improving the blood microcirculation to improve the metabolic rate in the impact tissue. The main difference between these different technologies is the magnitude of change.

Research frontiers

In the recent years most of the studies in the field of non-invasive body contouring treatments concentrating on the ability to reduce fat volume with significant circumferential reduction achieved *via* several treatment without pain, complications and downtime.

Innovations and breakthroughs

This is a first published study conducted with multi-polar radiofrequency (RF) handpiece (V-FORM) which based on channeling optimized RF energy (CORE) technology. For the authors' knowledge, it was also the first study that examined the correlation between initial body temperature, moisture level, skin impedance and circumferential reduction.

Applications

The data in this study suggested that treatment with multi-polar RF based on CORE technology can achieve high percentage of circumferential reduction also among patient with BMI higher then 30, which was common limitation for most of RF based treatments.

Terminology

Multi-polar RF configuration is a system that has more than two typical bi-polar electrodes. In such configuration, each pair of electrodes acts as bi-polar RF, but more than one pair is available making the heating procedure faster and homogeneous.

Peer-review

This is an interesting paper regarding the use of radiofrequency technology, with regards to safety and efficacy. Overall, the study methodology was adequate, and the results were significant.

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CASE REPORT

Papular mycosis fungoides: Six new cases and association with chronic lymphocytic leukemia

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Author contributions: Vonderheid EC and Kadin ME designed the report; Telang GH performed the histologic and immunopathologic studies; Vonderheid EC collected the patients' clinical data; Vonderheid EC, Kadin ME and Telang GH analyzed the data and wrote the paper.

Institutional review board statement: The study was approved by the Johns Hopkins Institutional Review Board.

Informed consent statement: Information about patients was obtained from an approved Cutaneous Lymphoma Registry and informed consent for clinical photography was obtained from all patients.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

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Abstract

Papular mycosis fungoides (MF) is a rare presentation of MF. Six illustrative cases of papular MF were retrospectively reviewed. Five of the cases studied by immunohistochemistry had variable numbers (range: 1%-20%) of CD30+ cells in the dermal infiltrate, a finding that is characteristic of lymphomatoid papulosis but may occasionally occur in typical early MF. Although none of our papular MF patients had progressive disease, lesions with relatively high numbers of CD30+ cells in 3 patients did not respond well to skin-directed treatments used for MF. Interestingly, these patients had evidence of co-existing clonal B cell populations in the blood (one with clonal B cell lymphocytosis and two with B-cell chronic lymphocytic leukemia). We conclude that: (1) papular MF may contain CD30+ cells, thereby causing confusion with lymphomatoid papulosis; and (2) papular MF, like more typical MF, may be associated with clonal B-cell proliferations including chronic lymphocytic leukemia.

Key words: Mycosis fungoides; Lymphocytosis; Chronic lymphocytic leukemia; Papule; Cutaneous lymphoma

Core tip: Mycosis fungoides presenting with papules

as the only clinical manifestation is a rare variant of the disease. To date only 16 cases of papular mycosis fungoides have been described in the literature and none had CD30+ cells. We report 6 additional cases, 5 with 1%-20% CD30+ cells. Three cases had co-existing clonal B cell lymphoproliferation (2 with chronic lymphocytic leukemia). The possible pathogenic relationship between mycosis fungoides and chronic lymphocytic leukemia is discussed.

Vonderheid EC, Kadin ME, Telang GH. Papular mycosis fungoides: Six new cases and association with chronic lymphocytic leukemia. *World J Dermatol* 2016; 5(4): 136-143 Available from: URL: http://www.wjgnet.com/2218-6190/full/v5/i4/136.htm DOI: http://dx.doi.org/10.5314/wjd.v5.i4.136

INTRODUCTION

Mycosis fungoides (MF), a great masquerader of other skin diseases, can present with varied types of lesions that are confused with infectious and drug related eruptions among others[1,2]. Recently, Kodama reported 6 cases of "papular MF" that presented with persistent papules that had the histopathologic features of MF but without typical patch/plaque MF lesions nor evidence of a lymphomatoid drug reaction[3]. Lymphomatoid papulosis (LyP) was excluded by the absence of spontaneous regression of lesions and lack of CD30+ cells in the dermal infiltrate. With follow up, 2 cases subsequently developed typical skin manifestations of MF (one developed MF patches only 2 mo after the diagnosis of papular MF).

At the time of this report, 10 additional cases of papular MF have been published (Table 1)[4-11]. Collectively, these papular MF cases (8 men, 8 women, ages, 27 to 83 years) are characterized by the following: (1) persistent papules, sometimes only a few millimeters in diameter, that did not enlarge into nodules, plaques or tumors; (2) Pautrier microabscesses in 8 of 14 cases; (3) a CD4+ immunophenotype in 8 cases and a CD8+ phenotype in 2 cases; (4) negative staining for CD30 in all 16 cases; (5) clonal T cells demonstrated in 7 of 8 cases; (6) subsequent appearance of typical patch or plaque lesions of MF in 3 cases including Kodama's 2 cases; and (7) an overall non-progressive clinical course.

Herein we report our experience with 6 additional cases of papular MF. Unlike reported cases, variable numbers of CD30+ cells were observed in the dermal infiltrate in 5 cases and 3 cases had evidence of co-existing clonal B-cell proliferations in the blood. The significance of these findings is discussed.

CASE REPORT

The registry of patients with cutaneous T cell lymphoma (1481 patients diagnosed with MF excluding its erythrodermic variant) that is maintained by one of us with approval of the Institutional Review Board at Johns Hopkins University was reviewed for cases that fulfilled the clinical-pathological criteria for papular MF as defined by Kodama[3]. Information obtained at the time of initial presentation, subsequent staging and follow up provide the basis of this report. This includes the results of histopathology, immunohistochemistry on corresponding frozen sections, and PCR amplification of T cell receptor gamma (TCR-γ) chain gene for T cell clonality on representative lesions.

The Surveillance, Epidemiology, and End Results (SEER)-9 registry, which captures data from 9.4% of the total United States population, was analyzed using SEER*Stat 8.2.1 software to determine the relative risk of developing chronic B-cell leukemia (ICD-O-3 Site C42.0, C42.1, C42.4 and ICD-O-3 code 9823/3) in patients initially diagnosed with MF (ICD-O-3 code 9700/3) and *vice versa* between 1973 and 2012. The statistical significance of the standardized incidence ratio (observed/expected) was determined using a Poisson distribution to calculate 95% confidence intervals.

Our retrospective review identified 6 patients who presented with persistent papules and/or small nodules with histopathologic features interpreted as diagnostic or consistent with MF (Table 2 and Figures 1-7). With follow-

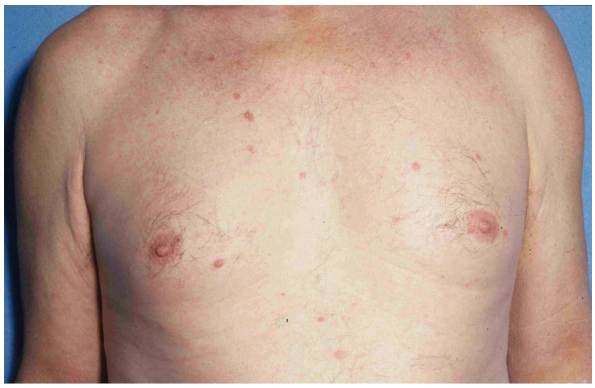

Figure 1 Patient 4 presented with a 6 mo history of persistent 2 to 8 mm papules of mycosis fungoides on the trunk and legs.

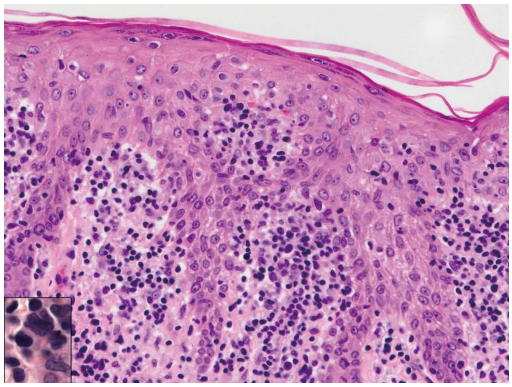

Figure 2 Skin specimen from patient 4 shows an acanthotic epidermis that contains atypical lymphocytes with hyperchromatic irregular nuclei (insert). The dermis has a superficial infiltrate composed of normal and atypical lymphocytes (H and E, × 400).

Table 1 Mycosis fungoides presenting as persistent papules in the literature

Case[1]	ARG; Dur	Distribution	Dermal infiltrate	Epidermal lymphocytes	Immunophenotype	PCR	Progression (time)[2]
Kodama1	57WM; NS	T	PV, F	Sm; PMAs	CD30-	ND	No
Kodama2	58WF; 2 yr	T, UE	Li, PV	Pleo Sm-med; No PMAs	CD4+30-	Pos	No
Kodama3	57F; Few mo	T, UE, LE	Li, PV	NS; No PMAs	CD30-	ND	Yes (3 yr)
Kodama4	41M; NS	LE	Li, PV	NS; No PMAs	CD30-	ND	Yes (2 mo)
Kodama5	59WM; 30 yr	T, UE, LE[3]	Li	NS; PMAs	CD30-	ND	No
Kodama6	61M; NS	T	PV	NS; PMAs	CD4+8-30-	ND	No
Uddin	31WF; 2 yr	T, UE, LE	Li, PV, SC, VA	NS; No PMAs	Mostly CD30-	ND	No
Martorell-Calatayud1	50WF; 2 yr	T[3]	A, P, Li, PV, F	Pleo Med-lg; PMAs	CD4+30-	Pos	No
Martorell-Calatayud2	55WF; 1.5 yr	T, LE[3]	NS	Sm-med; No PMAs	CD4+30-	Neg	No
Liu	27AM; NS	T[3]	Li	NS; PMAs	CD4+8-30-	ND	No
Neri	47WF; 1 yr	UE, LE	PV	Sm-med CL; PMAs	CD4-8+7+30-	Pos	No
Noe1	83WF; 3 yr	T, UE, LE	PV	NS; PMAs	CD4+30-	Pos	No
Noe2	65WF; 1mo	T	Li, PV	NS	CD30-	ND	Yes (NS)
Brajon	63WM; 10 mo	T, UE, LE	Li, PV	CL; NS	CD4+8-30-	Pos	No
Santamarina-Albertos	55WM; 1 yr	LE	Li	Sm-med CL; NS	CD4+30-	Pos	No
Balta	35WM; 2 yr	T, UE, LE	A, PV	NS; PMAs	CD4-8+30-	Pos	No (10 mo)

[1]References: [3-11]; [2]Time to progression of disease; [3]Some grouping or clustering of lesions. ARG: Age, race, gender; Dur: Duration to disease; PCR: Polymerase chain reaction for rearrangement of T cell receptor gamma chain; NS: Not stated; T: Trunk; UE: Upper extremities; LE: Lower extremities; Li: Lichenoid; PV: Perivascular; A: Acanthosis; P: Parakeratosis; F: Fibrosis; VA: Vacuolar alteration; SC: Subcutaneous; Sm: Small sized; Med: Medium sized; Lg: Large sized; Pleo: Pleomorphic; PMA: Pautrier microabscess; CL: Lymphocyte with cerebriform or infolded nuclei.

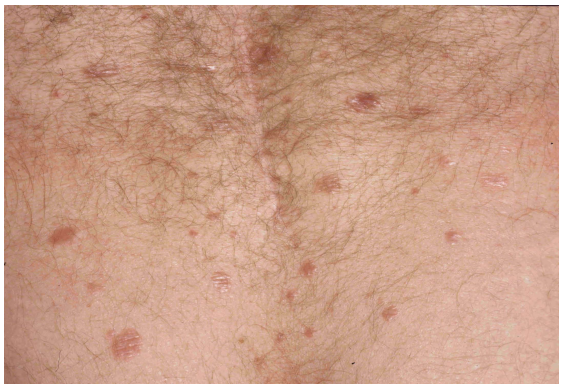

Figure 3 Persistent 2 to 14 mm papules of mycosis fungoides scattered on trunk and legs of patient 5.

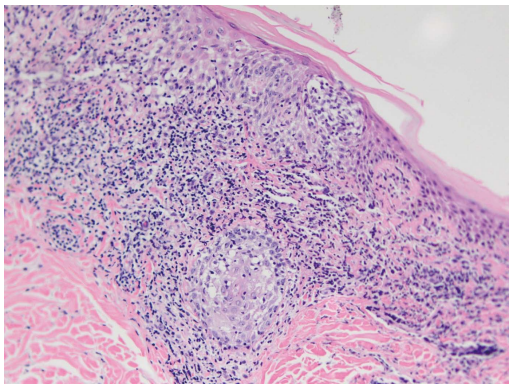

Figure 4 Skin specimen from patient 5 shows a moderately dense lichenoid infiltrate, wiry bundles of collagen in a thickened papillary dermis, and follicular mucinosis. Numerous atypical lymphocytes, some with large irregular nuclei, are located within the epidermis, both as solitary units and in aggregates, and dermal infiltrate (H and E, × 400).

up, none of these papular MF patients developed typical lesions of MF nor had disease progression. Pautrier microabscesses were described in skin specimens from 3 patients, and the immunophenotype of the neoplastic cells of 5 studied cases was CD4+CD8-. A dominant T cell clone was demonstrated by PCR in 3 cases.

Notably, all 5 patients evaluated for CD30 expression had variable numbers of scattered atypical CD30+ cells in the dermal infiltrate (estimated range: 1%-20%), a finding that suggested the possibility of type A LyP with epidermotropic T cells or possibly type B LyP. This was particularly true for the specimen from patient 2 (Figure

Table 2 Six additional patients with papular mycosis fungoides

Pt	ARG; Dur[1]	Lesions and Size (mm)	Distribution	Dermal Infiltrate	Epidermal Lymphocytes	Immunophenotype[2]	TCR-γ (method)	Course and Status (Duration FU)
1	68WM; 15 mo	Pa (1-2)	T, UE, UE	PA, VA, F, PC, Eos, LVC	Focal basilar Ep, Med CLs; No PMAs	ED: NS D: CD4 > CD8, CD30 10%	Pos Sk + Bd (SSCP)[3]	Controlled on prednisone; developed pancytopenia; DwD (99 mo)
2	47 WM; 19 yr	Pa (3-5)	H/N, T	A, PV, F, Eos, PC, MtF, LVC	Focal basilar Ep, Med-lg CLs; PMAs	ED: CD4+8-7-62L-30- D: CD4 90%, CD8 < 10%, CD7< 10%, CD62L < 1%, CD30 5%-10%	Pos Sk + Bd (DGGE)[3]	Poor or partial response to PUVA, MTX, isotretinoin, XRT, IFNα; DwD (171 mo)
3	57 WF; 5 yr	Pa (2-5)	LE, UE	P, A, Li, PV, CLs	Basilar Ep, CLs; No PMAs	ED: CD4+8-7+62L+30+/-[4] D: CD4 80%, CD8 20%-30%, CD7 40%, CD62L 50%, CD30 1%-2%	Neg (DGGE)	PUVA/NBUVB: CR; breast CA; RA, HT; A, NED (156 mo)
4	68 WM; 6 mo	Pa (2-8)	T, LE	A, Li, F, EE, Neu (v), CLs	Diffuse Ep, Med CLs; No PMAs	ED: CD4+/-8-7+62L-30- D: CD4 60%-70%, CD8 20%, CD7 70%, CD62L 70%, CD30 1%-2%	Pos (DGGE)	PUVA: CR ; no progression; AwD (210 mo)
5	58 WM; 2 mo	PaNd (2-14)	T, LE	Sp, Li, F, FM, CLs	Basilar Ep, Med-lg CLs; PMAs	Not available	Neg (SSCP)[5]	TopHN2: CR; No progression; A, NED (171 mo)
6	81 WM; 15 mo	PaNd (5-15)	T, LE	Li, F, CLs, MtF	Diffuse Ep, Med-lg CLs; PMAs	ED: CD4+8-7-62L-30- D: CD4 99%, CD8 1%, CD7 10%, CD62L 99%, CD30 20%	Neg (DGGE)[3,5]	PUVA: PR; DwD/MI (12 mo)

[1]Duration: Time from onset of disease to evaluation; [2]Estimated percentage of positively labeled cells in dermal infiltrate (frozen sections). CD2, CD3, and CD5 expressed by all cases (data not shown); [3]Clonal B-cell population detected by flow cytometry for patients 1, 2 and 6 and confirmed by PCR for patients 1 and 2 (see text for details); [4]30% of epidermotropic T cells expressed CD30; [5]Blood sample also negative for T cell clone. Pt: Patient; ARG: Age, race, gender; TCR-γ: T-cell receptor gamma chain rearrangement; FU: Follow up; Pa: Papule; Nd: Nodule; T: Trunk; UE: Upper extremity; LE: Lower extremity; A: Acanthosis; Sp: Spongiosis; P: Parakeratosis; VA: Vacuolar alteration; Ep: Epidermotropism; Li: Lichenoid (band-like); PV: Perivascular; PA: Periadnexal; PDE: Papillary dermal edema; F: Fibrosis; FM: Follicular mucinosis; Neu (v): Neutrophils in vessels; PC: Plasma cells; Eos: Eosinophils; EE: Extravasated erythrocytes; CL: Lymphocytes with cerebriform or infolded nuclei (mycosis cells); MtF: Mitotic figures; LVC: Lymphocytes with vesiculated nuclei and prominent nucleoli; PMA: Pautrier microabscess; Sm-med: CLs with small-medium sized nuclei (5 to 7 μm in diameter); Med-lg: CLs with medium-large sized nuclei (7 to 9 μm in diameter); ED: Epidermis; D: Dermis; >: Greater than; <: Less than; NS: Not stated; Sk: Skin; Bd: Blood; DGGE: Denaturing gradient gel electrophoresis; SSCP: Single-stranded conformation polymorphism; MTX: Methotrexate; XRT: Local field radiation therapy, IFNα: Interferon alfa; PUVA: Methoxsalen-ultraviolet A photochemotherapy; NBUVB: Narrow band ultraviolet B phototherapy; TopHN2: Topical mechlorethamine; CA: Carcinoma; RA: Rheumatoid arthritis; HT: Hashimoto's thyroiditis; MI: Mycocardial infarction; AwD: Alive with active disease; DwD: Dead with active disease; A: NED, alive, no evidence disease; LTF: Lost to follow up.

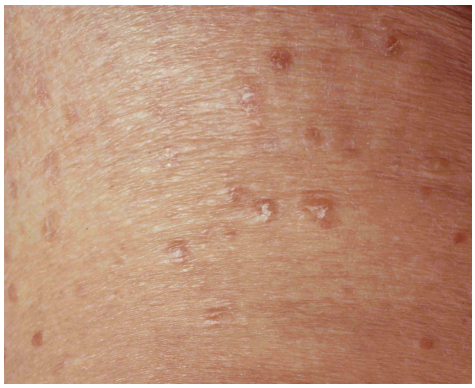

Figure 5 Patient 6 presented with a 15 mo history of persistent papules and small nodules, some with scaling, disseminated on the trunk and legs.

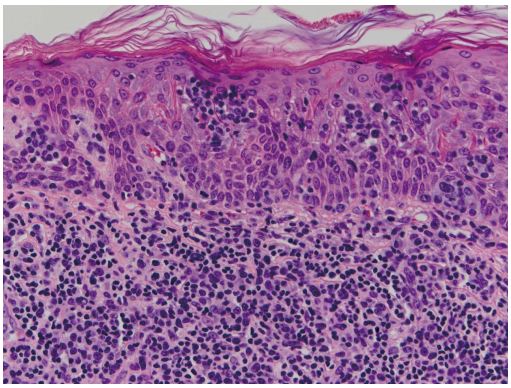

Figure 6 Skin specimen from patient 6 shows typical histopathologic features of mycosis fungoides. Nests of medium to large sized neoplastic lymphocytes with pleomorphic and cerebriform nuclei are observed within the epidermis (Pautrier microabscesses) and adjacent superficial dermis (H and E, × 400).

7). However, his skin lesions did not spontaneously regress as expected in LyP. In addition, CD30 also was expressed by 30% of the epidermotropic CD4+T cells of patient 3 (discussed below). Therefore, other than persistence of lesions, the histo-immunopathologic findings of papular MF overlap with those of LyP[12,13].

Table 3 Frequency of B-cell chronic lymphocytic leukemia occurring after a diagnosis of cutaneous T cell lymphoma

Ref.	Cohort	No. patients (Dx)	No. secondary B-CLL (%)
Olsen *et al*[27]	One institution	63 (CTCL)	0 (0)
Kantor *et al*[28]	One institution	519 (MF)	2 (0.39)
Väkevä *et al*[29]	Finnish cancer registry	319 (MF/SS)	1 (0.3)
Barzilai *et al*[24]	Two institutions	398 (MF)	2 (0.50)[1]
Huang *et al*[30]	One institution	429 (MF/SS)	1 (0.23)
Huang *et al*[30]	SEER-9 registry	1798 (MF/SS)	0 or 4 (0 or 0.22)[2]
Hallerman *et al*[31]	One institution	62 (CTCL)	0 (0)
Brownell *et al*[32]	One institution	672 (CTCL)	0 (0)
Hodak *et al*[33]	One institution	343 (MF)	2 (0.59)
Hodak *et al*[33]	Israeli population registry	683 (MF)	1 (0.15)
Lindahl *et al*[34]	Population-based	386 (MF)	0 (0)[3]
Current study	SEER-9 registry	3,977 (MF)	10 (0.25)

[1]One case with B-CLL preceding MF was excluded; [2]Surveillance, Epidemiology, and End Results (SEER)-9 Cohort between 1984 through 2001 included 4 cases of leukemia, not defined; [3]The 2 cases of hematologic cancer exclusive of non-Hodgkin lymphoma in this cohort were not B-CLL (Lindahl, personal communication, 2016). MF: Mycosis fungoides; SS: Sézary syndrome; CTCL: Cutaneous T cell lymphoma; B-CLL: B cell chronic lymphocytic leukemia; Dx: Diagnostic groups in cohort.

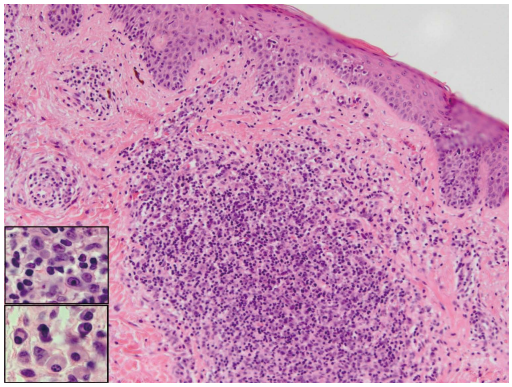

Figure 7 Skin specimen from patient 2 shows a perivascular and dense nodular infiltrate in the superficial and mid-dermis. A fibrotic papillary dermis and scattered epidermotropic lymphocytes aligned along the basal layer in the absence of spongiosis (H and E, × 400). The dermal infiltrate is composed of lymphocytes, some with large hyperchromatic cerebriform nuclei, large immunoblast-like cells (top insert), small clusters of plasma cells (bottom insert), and occasional eosinophils.

A second observation is that 3 of the papular MF patients had evidence of an associated clonal B-cell lymphoproliferation. Patient 1 had a T cell clone in skin and blood plus 6% of blood lymphocytes with a CD5+CD19+CD23+ phenotype and B cell clone demonstrated by PCR of the IgH gene in the blood, but not the skin. The small B cell population remained unchanged with follow-up and is therefore classified as clonal B cell lymphocytosis. Patient 2 had a T cell clone in skin and blood plus 65% of his blood lymphocytes were CD19+CD20+ B cells (absolute lymphocyte count: 770 cells/mm^3) and evidence of a B cell clone by PCR in the blood but not the skin. A subsequent bone marrow analysis revealed 20% B cells co-expressing CD5 and CD23 characteristic of chronic lymphocytic leukemia (B-CLL). Patient 6 also had a B cell clone in the blood by flow cytometry (21% of lymphocytes with a CD5+CD19+CD20+ phenotype; absolute lymphocyte count: 2490 cells/mm^3) but a negative PCR study when initially evaluated. However, a diagnosis of B-CLL was confirmed 6 mo later. These patients with clonal B cells tended to have higher percentages of CD30+ cells in their skin lesions and their response to treatment was partial or transitory compared to the other papular MF cases.

DISCUSSION

Papular MF is a very rare presentation of the disease, occurring in 0.4% of non-erythrodermic MF cases referred to our center. However, our patients differed from published cases with regard to the presence of atypical CD30+ cells in the dermal infiltrate in 5 studied specimens. Specimens from 3 patients had estimated numbers of dermal CD30+ cells that ranged from 5% to 20% such that LyP would be an alternative diagnosis. However, unlike LyP as currently defined, these lesions did not undergo spontaneous regression. Atypical CD30+ cells may also be encountered in clinically early lesions of MF so this finding does not exclude papular MF from the differential diagnosis[14]. The clinical significance of CD30+ cells in this context is unclear. It has been reported that CD30 expression in non-transformed patch or plaque phase MF has an adverse prognostic significance[14]. Although none of the patients in our small series developed more typical lesions of MF nor had disease progression, the 3 cases with 5% or more CD30+ cells in the dermal infiltrate did not respond adequately to various skin-directed therapies used to treat early MF.

An unexpected and previously unreported observation was that 3 patients with papular MF had an associated B-cell lymphoproliferative disorder (one with monoclonal B cell lymphocytosis and two with B-CLL). This raises the possibility that some of our papular MF cases might be examples of pseudo-MF reactions associated with B-CLL as described by Ingen-Housz-Oro[15]. In that paper, the

authors reported 4 patients that presented with localized papules in concert with B-CLL. Three patients were diagnosed to have a pseudo-MF reaction and one had papular MF. All cases had evidence of folliculotropism by lymphocytes and 3 had follicular mucinosis including the papular MF case. Of note, a T cell clone could not be demonstrated by PCR of the TCR-γ chain gene in all cases, whereas clusters of neoplastic B cells were observed in 3 cases including the papular MF case. CD30 staining was not performed. Therefore our papular MF cases differ from Ingen-Housz-Oro's cases in several ways: (1) in our patients, lesions were more widespread; (2) folliculotropic T cells and a B cell component in the infiltrate were not present; and (3) T cell clonality was demonstrated in two cases. Of interest, mature appearing plasma cells were observed in the dermal infiltrate of skin specimens obtained from patients 1 and 2 who had evidence of clonal B cells in the blood but not the skin (Figure 7). In addition, a prior skin specimen from patient 6 and studied elsewhere also showed numerous plasma cells. This phenomenon may be the result of a homing process as suggested by Ingen-Housz-Oro[15].

The association of MF and B-CLL may not be a fortuitous event. A review of the literature uncovered 23 cases of classic patch, plaque or tumor phase MF (erythrodermic MF excluded) co-existing with B-CLL[15-26]. Of interest CD30 staining was performed on skin specimens from only 2 cases and both were reported to be negative. Nevertheless, it has not been established that the risk of developing secondary B-CLL in MF patients is significantly higher than for the general population (Table 3)[27-34].

In the SEER-9 database, 1973 to 2012, there are 3977 cases coded as MF as the primary cancer for analysis. Of these, B-CLL was subsequently diagnosed in 10 cases compared to an expected frequency of 6.77 cases. Therefore, the relative risk (observed/expected) is 1.48 (95%CI: 0.71-2.71). Conversely, of 34160 cases with B-CLL as the primary cancer, 7 developed MF as a second cancer for a relative O/E of 7/4.02 or 1.74 (95%CI: 0.7-3.59). Although these relative risks are increased, they are not statistically significant. However, the possibility that the number of MF cases in the SEER registry might be under reported must be considered for several reasons: (1) some MF cases may be diagnosed as cutaneous T cell lymphoma and therefore coded by registrars as such (ICD-0-3 code 9709/3); (2) cases of MF and B-CLL that are diagnosed concurrently are coded separately as primary cancers; and (3) perhaps not all cases of MF are reported to the SEER registry by private dermatologists or dermatopathology laboratories[35].

With regard to the first point, of 1304 patients coded initially as having cutaneous T cell lymphoma, 18 patients were subsequently coded as MF compared to an expected number of 0.15. The observed/expected ratio was 121.58 (95%CI: 72.06-192.15) was significantly high ($P < 0.05$). It is therefore conceivable but not proven that some patients with MF might be coded initially in the broader diagnostic category of cutaneous T cell lymphoma.

Incidentally our review also uncovered a case reported in 1983 that was characterized by disseminated therapeutically resistant papules with histopathologic features of MF in a patient with B-CLL[36]. We propose this case could represent the first example of papular MF associated with B-CLL.

The underlying basis for the uncommon but well documented association of MF and other forms of cutaneous T cell lymphoma with various B cell lymphoproliferations is unclear. Our hypothesis, which also has been suggested by others[18,19], is that an inherited genetic attribute that predisposes a patient to lymphoma (such as a nucleotide polymorphism)[37] or an acquired mutation is present at the level of the common lymphoid progenitor cell. If additional genetic alterations that promote lymphoma occur later in both the B and T cell developmental pathway, this would account for the observed associations of various T and B cell lymphoproliferations. It would also explain why B-CLL may precede, follow or present concurrently with cutaneous T cell lymphoma and the increased familial risk of lymphomas in family members of patients with cutaneous T cell lymphoma[38]. The increased risk of non-hematologic cancers in patients with cutaneous T cell lymphoma could be explained by the immunosuppression related to the disease and/or use of oncogenic treatments[27-30,33,34,39].

Alternatively, the interaction between stimulatory ligands such as CD30-CD30L and CD40-CD40L expressed by T and B cells may provide an explanation for the co-existence of T and B cell lymphoproliferative diseases in susceptible patients. For example, the interaction between CD40L, which is expressed by neoplastic T cells of MF[40], and CD40, which is constitutively expressed by B cells, could result in up-regulation of genes involved in B cell survival and proliferation[41,42]. The frequent expression of CD30 in some of our papular MF cases (and most LyP variants) with possible increased levels of soluble CD30 in the blood that we have observed in typical early MF patients could in theory contribute to the risk of developing B-CLL[43-45].

We conclude that MF may rarely present with persistent papules, but that there is considerable clinical and histo-immunopathologic overlap with LyP including a favorable prognosis[12,13]. Indeed the main difference is the persistence of lesions in papular MF and spontaneous regression of lesions in LyP. Considering that typical MF lesions may undergo partial or even complete regression[46], we wonder if the differences between papular MF and LyP may be related to differences in factors that mediate lesion regression such as the host immune response. In addition, in this small series, there appears to be an association of papular MF with B-cell CLL that requires confirmation and further investigation.

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relative risk of secondary B-CLL in patients with MF.

COMMENTS

Case characteristics

Mycosis fungoides (MF), a great masquerader of other skin diseases, can present with varied types of lesions that are confused with infectious and drug related eruptions among others.

Clinical diagnosis

Lymphomatoid papulosis (LyP) was excluded by the absence of spontaneous regression of lesions.

Differential diagnosis

The registry of patients with cutaneous T cell lymphoma (1481 patients diagnosed with MF excluding its erythrodermic variant) that is maintained by one of the authors with approval of the Institutional Review Board at Johns Hopkins University was reviewed for cases that fulfilled the clinical-pathological criteria for papular MF as defined by Kodama.

Imaging diagnosis

This retrospective review identified 6 patients who presented with persistent papules and/or small nodules with histopathologic features interpreted as diagnostic or consistent with MF

Experiences and lessons

Papular MF is a very rare presentation of the disease, occurring in 0.4% of non-erythrodermic MF cases referred to their center.

Peer-review

This is an interesting case series of papular mycosis fungoides. The authors described the clinical and histological features of this clinical entity, and its association with chronic lymphocytic leukemia. In general, the manuscript is well-written, and the content is clinically relevant and scientifically informative.

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