Co-occurrence of pemphigus vulgaris and multiple endocrine neoplasia type 1: a case report and review of literature

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Multiple endocrine neoplasia type 1 (MEN1) is a rare, autosomal dominant hereditary syndrome caused by mutations of the *MEN1* tumor suppressor gene. We describe a patient with a prior confirmed diagnosis of pemphigus vulgaris (PV), who presented with new cutaneous manifestations that led to the diagnosis of MEN1. A man in his early forties with a history of PV from 11 years ago presented with some cutaneous lesions six months ago, diagnosed as angiofibroma and collagenoma. Moreover, he suffered from recurrent renal stones and gout for several years. Laboratory analysis showed hypercalcemia, which led us to confirm the diagnosis of a parathyroid adenoma by sestamibi scintigraphy. Contrast-enhanced computed tomography (CT) of the abdomen revealed hyper-enhancing pancreatic lesions while the patient had no related symptoms. Thus, the clinical diagnosis of MEN1 syndrome was settled, and the patient underwent surgical and medical management. A hitherto unreported co-occurrence between MEN-1, as a hereditary syndrome, and PV, as an autoimmune bullous cutaneous dermatosis, opens a hazy challenging issue: whether MEN-1 has any association with autoimmune bullous cutaneous diseases like PV or increases the incidence of such conditions.

Keywords: multiple endocrine neoplasia type 1, cutaneous manifestations, pemphigus vulgaris

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INTRODUCTION

Multiple endocrine neoplasia type 1 (MEN1) was first described by Wermer in 1954. It is a rare autosomal dominant disorder caused by *MEN1* gene mutations on chromosome 11q13, predisposing the patient to endocrine and non-endocrine neoplasia [1]. The incidence rate is about one in 30,000 individuals without any sex or racial predilection. A significant increase in premature death is presumed for individuals suffering from MEN1 syndrome. MEN1-associated malignancies generally account for approximately 30% of deaths in such patients [2].

The diagnosis of MEN1 can be made clinically, or directly with genetic testing for a *MEN1* mutation. The clinical diagnosis of MEN1 is usually made in most patients' fourth decade of life and confirmed when at least two specific tumors occur or a single tumor is detected in patients with a positive family history [2].

Tumors associated with MEN1 are hormone-secreting parathyroid, pituitary gland, and gastro-entero-pancreatic (GEP) tumors. Other endocrine and non-endocrine tumors were recently linked with MEN1, including carcinoids (lung, thymus, and gastric), central nervous system tumors, adrenal tumors, smooth muscle tumors, and skin tumors [2-7].

Among several organ involvements, skin lesions are of particular note due to the occurrence rate

of 88% among MEN1 patients [4]. Also, skin tumors are the first noticed manifestation of the disease during most clinical examinations and may help the earlier diagnosis of the disease before the manifestations of hormone-secreting tumors. Thus, skin manifestations of MEN1 syndrome should be well described.

Cutaneous manifestations include:

- Facial angiofibromas: Benign tumors consisting of non-regressing acneiform papules present in about 85% of affected individuals, arising from connective tissues and blood vessels. Compared to similar lesions in tuberous sclerosis, facial angiofibromas in MEN1 tend to be fewer and smaller and may extend across the vermilion border of the lips.
- Collagenomas: These lesions frequently present as multiple, skin-colored, sometimes hypo-pigmented cutaneous nodules with a symmetrical arrangement on the neck, trunk, and upper limbs. Collagenomas are present in about 70% of affected individuals and typically are rounded, asymptomatic, and firm-elastic, ranging from a few millimeters to several centimeters in size [3].
- Lipomas: Benign fatty tissue tumors, detected approximately in 30% of affected individuals. Lipomas can be found in any fat tissue and are mostly subcutaneous or, rarely, visceral [4].
- Other skin manifestations include café-au-lait macules (38%), as well as multiple gingival papules (6%), and confetti-like hypopigmented macules (6%). Rare reports of skin malignancies like melanoma have been published [3,4]. However, an increased risk of skin malignancies among individuals with this syndrome remains unclear.

There is no report of the co-occurrence of any autoimmune skin bullous disease with MEN syndromes.

CASE PRESENTATION

A 41 years old man with a confirmed history of pemphigus vulgaris (PV) from eleven years ago presented to our dermatology clinic due to some new skin lesions from six months ago, differing from the lesions related to PV. He was under treatment with prednisolone (20 mg/12.5 mg every other day) and oral methotrexate (12.5 mg weekly) at the time of reference, and the disease was controlled with no new lesions for six months. In skin examination, small dome-shaped papules on the face (Figure 1) and soft skin-colored dome-shaped nodules of various sizes on the axilla, lower portions of the abdomen, and groins (Figure 1) were observed. He declared the same skin masses in his mother, who died due to unknown reasons in her fifties. Skin biopsy of face papules revealed angiofibroma and trunk lesions were reported as collagenoma and fibroma. Additionally, he had two episodes of calcium-rich nephrolithiasis in his late twenties. Both hypercalcemia (10.7 mg/dl) and hyperparathyroidism (186 p/ml) were observed during the course of his outpatient endocrinology workup. Thereupon, nuclear medicine sestamibi scan of the neck revealed a single focus with persistently increased radiotracer activity within the inferior right thyroid gland, suggesting a parathyroid adenoma. Suspicious of MEN syndrome, a more detailed patient's history was obtained. The patients stated that an unknown abdominal mass in his mother led to her death ten years ago. Given this history, as well as laboratory and imaging findings, a presumed workup in order to diagnose MEN1 syndrome was initiated. Thus, while a parathyroidectomy was indicated, it was postponed due to the suspected MEN1 syndrome.

The patient was further evaluated by means of abdominal and pelvic contrast-enhanced computed tomography (CT). An 80×100 mm hypodense mass in the body of the pancreas and a 13 mm hypodense mass in the pancreas tail was observed, consistent with neuroendocrine tumors. Hence, the patient was admitted to the gastroenterology ward in order to obtain samples by means of endo-sonography besides further assessment. However, he did not complain of any upper abdominal pain, gastroesophageal reflux, diarrhea, peptic ulcers, or hypoglycemic symptoms. While fine needle aspiration (FNA) reported hemorrhagic fluid and no cellular components, the patient developed acute pancreatitis after endo-sonography. He was discharged after one week and refused to undergo further diagnostic intervention regarding the pancreas masses. The patient had no symptoms of an intracranial mass. Moreover, MRI of the brain as well as pituitary hormonal assays revealed no pathologic findings.

Genetic testing as well as surgical planning of

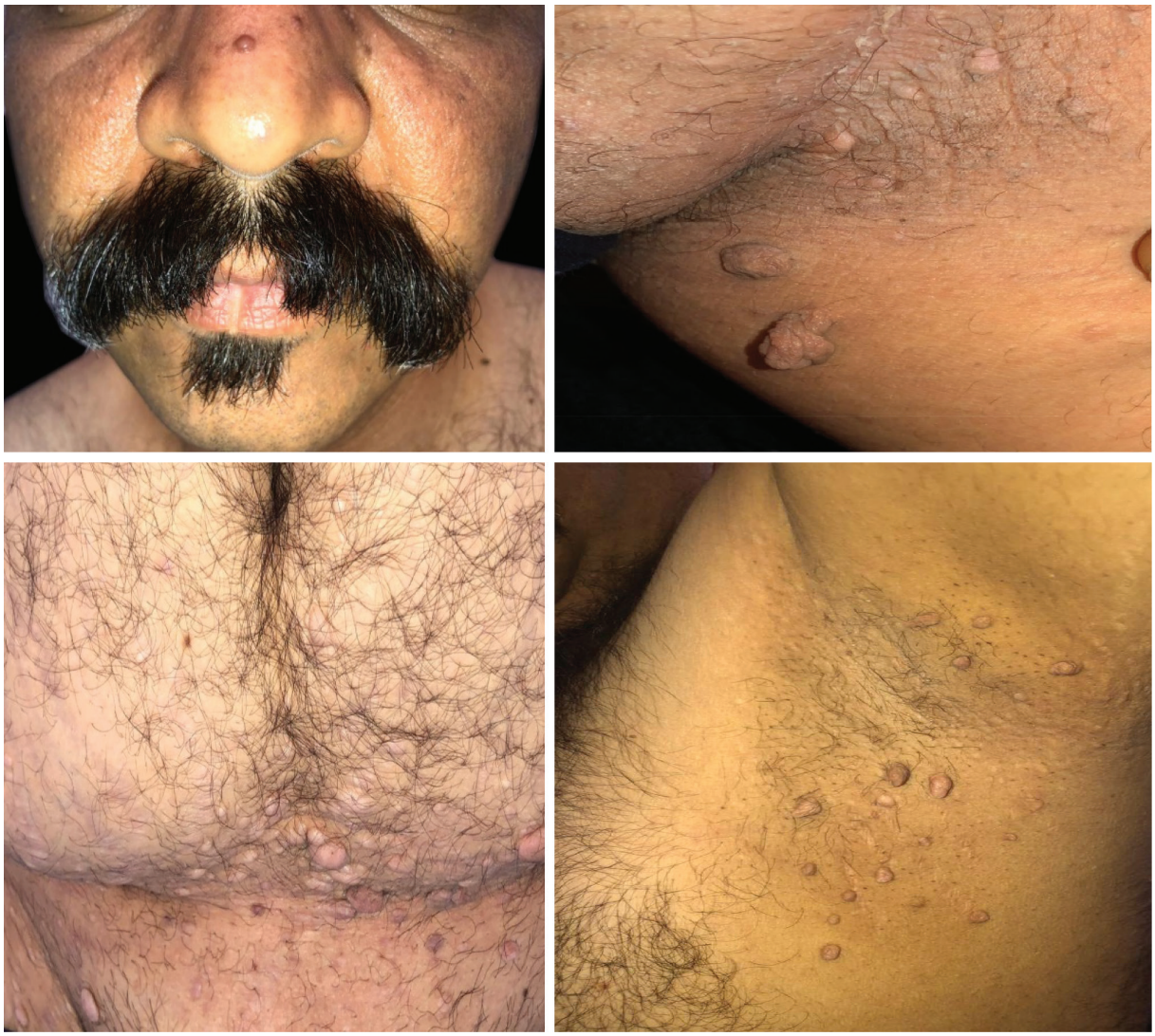

Figure 1. Small dome-shaped papules on the face, diagnosed as angiofibromas. Soft, skin-colored, dome-shaped nodules on the axilla and lower portions of the abdomen and groins, diagnosed as collagenomas.

parathyroidectomy are underway and postponed due to the patient's hospitalization for pancreatitis.

At the time of writing, conservative therapy led to the relative improvement of the patient's symptoms. Management of the pancreas lesions remains controversial, and further discussions between the patient, endocrinologists, and surgeons are ongoing.

DISCUSSION

Recent studies have raised the interest in MEN1 pathologies, in addition to endocrine features. The first report on cutaneous manifestations of MEN1 syndrome was published in 1977 by Darling *et al.*, describing the association of MEN1 with some cutaneous tumors such as angiofibromas, collagenomas, lipomas, and 'cafe au lait macules [4]. The association of MEN1 with angiofibromas was formerly confirmed. Recently, skin tumors, including angiofibromas and collagenomas as well as lipomas and melanomas, have been proposed as potentially useful markers of MEN1 [8].

Skin manifestations of MEN1 develop when the inactivating mutation of the *MEN1* gene on chromosome 11q13 adds to the germline mutation, leading to cellular replication [9]. The same mutations of this gene have been formerly described in

melanomas [9,10], sporadic brown fat tumors [11], angiofibromas [12], and sporadic endocrine tumors [8].

Vidal and colleagues (2007) studied skin manifestations among 9 MEN1 patients and 20 non-carries first-degree relatives. They reported the occurrence of angiofibromas in 22.2% of the patients and did not find any collagenomas [8]. The results were relatively lower than similar studies, which reported the prevalence of angiofibroma in MEN1 syndrome as 43–88% [4,13]. Our patient had dome-shaped papules on the face and skin-colored nodules on the trunk, subsequently diagnosed as an angiofibroma and a collagenoma, respectively. No gingival papules, confetti-like hypomelanotic macules, and lipomas were observed on the patient's skin.

The diagnosis of MEN1 can be confirmed clinically or directly with genetic testing for a *MEN1* mutation. Our patient met the clinical criteria for diagnosis, as he had a history of a parathyroid adenoma and a newly discovered pancreatic tumor. Early presentation of the tumors as well as the positive family history on his mother's side suggested familial MEN1.

The most common tumor in MEN1 patients is a parathyroid adenoma, occurring in 90% of patients [2]. Primary hyperparathyroidism presents with nephrolithiasis, hypercalcemia, and osteitis fibrosa cystica. The onset age is rather earlier among patients with MEN1 syndrome, typically at about 20-25 years compared with 55 years of age in patients without this syndrome [14]. Although our patient presented in his early forties, he had a previous experience of nephrolithiasis during his late twenties. Also, during workup, both the patient's parathyroid hormone and serum calcium levels were elevated.

Initial evaluations of hyperparathyroidism include an ultrasound to detect an underlying parathyroid adenoma, followed by a nuclear technetium Tc-99m sestamibi scintigraphy for confirmation [15]. Typically, surgery is the standard treatment of parathyroid adenomas (either a total or subtotal parathyroidectomy with the removal of the overactive glands); however, it should be noted that recurrent/persistent hypercalcemia will probably occur after subtotal surgery [16]. MEN1 patients should be screened annually for primary hyperparathyroidism with the assessment of serum calcium and parathyroid hormone levels. In our patient, however, the parathyroid adenoma was identified by means of sestamibi scintigraphy. Surgical intervention of the adenoma was postponed due to an unsuccessful biopsy of the pancreatic tumor.

The prevalence of entero-pancreatic islet tumors in MEN1 varies from 30% to 75% and can affect approximately 80% of the patients in autopsy studies. Gastrinomas are diagnosed in 40% of the patients, causing Zollinger-Ellison syndrome and hypergastrinemia.

Gastrinomas, the most common GEP tumor in MEN1 syndrome, are often multiple and small (less than 0.5 cm), mainly situated in the duodenal submucosa. The prevalence of metastases is estimated at around 50%. Hypoglycemia may also occur due to insulinomas. Insulinomas are usually diagnosed approximately 10 years earlier among MEN1 patients than the sporadic cases. Other rare functioning entero-pancreatic islet tumors like glucagonomas, somatostatinomas, and VIPomas are also reported among MEN1 patients. Nevertheless, the frequency of non-functioning GEP tumors in MEN1 is higher (54.9%) than previously thought [17].

The incidence of pituitary tumors among MEN1 patients varies from 10% to 60%. The pituitary tumors are mainly microadenomas in most patients. Prolactin-secreting tumors (prolactinoma) are the most common (20%) pituitary tumor in MEN1 [17].

Bilateral adrenal tumors/hyperplasia may occur in 20–40% of individuals with MEN1, most of which are non-functional. Carcinoid tumors can be found in 10% of patients and originate from the foregut. Thymic carcinoids are mostly diagnosed in males and remain asymptomatic until an advanced stage [17]. The brain MRI of our patient showed no pathologic conditions. Also, the abdomen/pelvis CT scan revealed pancreatic masses. However, follow-up imaging studies should be considered in the future.

The co-occurrence of PV and MEN has not been previously reported in the literature. Hence, a possible common genetic/immune pathway has not been described yet. The genetic predisposition of PV, as an autoimmune bullous dermatosis, has not been precisely determined. The Human Leukocyte Antigen (HLA) class I and II molecules play a crucial role in the recognition of antigenic peptides by T cells. Moreover, a couple of HLA alleles including HLA-DQB1_0503 (in non-Jewish populations) and

HLA-DRB1_0402 (in Jewish people) have been reported to have a strong association with PV [18].

Autoimmune comorbidities are more likely to develop among patients with autoimmune diseases. PV is associated with autoimmune thyroiditis, systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, and type 1 diabetes [19]. Also, the possible association of PV and polyendocrine or Autoimmune Polyglandular Syndrome (APS) has been mentioned [20]. However, evidence is still contradictory in proving the association of PV with hematological and non-hematological neoplasms. According to two previous studies, the frequency of non-Hodgkin's lymphoma as well as leukemia were demonstrated to be 50% higher than expected among PV patients [21,22]. Moreover, the co-occurrence of MEN1 and APS was previously documented as case reports, implying the association of MEN1 with autoimmune diseases [23]. According to the above explanations, our hypothesis of the relationship between MEN1-as an inherited syndrome and PV as an autoimmune skin bullous disease can be justified.

The autoantibodies-antigens binding plays the main role in the blister formation of PV. The autoantibodies in PV, including anti-desmoglein (Dsg) 1 and anti-Dsg 3, are both members of the cadherin supergene family and maintain intercellular adhesion of stratified squamous epithelia. Besides, several cell signal transductions are induced by antibody bindings that lead to blister formation in PV, involving c-Myc, p38 mitogen-activated protein kinase (MAPK), caspases, epidermal growth factor receptor, and mitochondria [24-26].

Through the immune pathway, the function and concentration of regulatory T cells (Treg) in patients with PV are abnormal. Moreover, the concentration of CD4+ Treg cells was shown to have a negative correlation with Th17 cells among patients with PV [18]. This immune imbalance might be a critical factor in progression of both PV and MEN1 in our patient due to immunoregulatory dysfunction. On the other hand, MEN-1, as a rare autosomal dominant syndrome, has a more explicit genetic etiology. It is caused by inactivating mutations of the MEN-1 tumor suppressor gene, and is frequently associated with some neoplastic lesions in the pancreas, duodenum, and parathyroid and pituitary glands [25]. Typically, tumors develop by mutations in both *MEN1* alleles; however, incomplete inactivation of the *MEN1* gene has also been detected in thymic and duodenal neuroendocrine tumors [27].

History of the affected parent is recorded in almost 90% of the patients, and the other 10% have a de novo *MEN1* germline mutation. The *MEN1* gene location on chromosome 11 (11q13) encodes the protein named menin [16]; however, menin's specific biological role has not yet been described [27]. More than 1,200 germline mutations have been described to date, spread over the entire coding zone of the *MEN1* gene with no significant hotspot or genotype-phenotype correlation [28].

Approximately 5–25% of MEN1 patients show no mutation in pre-described coding regions; it is postulated that mutations may possibly occur in untranslated regions or promoters [28]. Thus, clinical/familial manifestations confirm the diagnosis of MEN1 in an individual. Our patient has not yet completed a genetic assay due to unwillingness and the high price of genetic studies in Iran. The screening of MEN1 mutations has several advantages, including confirmation of the clinical diagnosis and identification of other family members who are carriers of mutations. Hence, early screening of at-risk individuals is becoming increasingly important.

CONCLUSION

We present the first report of the co-occurrence of an autoimmune immunobullous dermatosis with the MEN syndrome. It takes time to make a definite comment on the association of autoimmune vesiculobullous dermatosis with MEN1 syndrome. Cutaneous lesions may be useful for detecting MEN1 individuals, and family members should be further investigated. It is suggested to dermatologists by the authors to consider further assessment for MEN1 syndrome among patients with immunobullous dermatoses in the case of related cutaneous manifestations or positive family history. Gene assays may help determine possible genetic predisposing factors in the coincidence of the diseases.

Conflict of interest: None declared.

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