European Review for Medical and Pharmacological Sciences 2020; 24: 8151-8159

Improvement of pure sensory mononeuritis multiplex and IgG1 deficiency with sitagliptin plus Vitamin D3

M. MAIA PINHEIRO[1,2], F. MOURA MAIA PINHEIRO[3], L.L. PIRES AMARAL RESENDE[4], S. NOGUEIRA DINIZ[2], A. FABBRI[5], M. INFANTE[5,6,7]

[1]UNIVAG University Center, Várzea Grande, Mato Grosso, Brazil
[2]Postgraduation Program in Biotechnology and Health Innovation, Professional Master Degree in Pharmacy, Anhanguera University of São Paulo, Brazil
[3]Hospital de Base – FAMERP, São José do Rio Preto, Brazil
[4]Oncovida – Oncology and Immunology Clinic, Cuiabá, Brazil
[5]Endocrine Unit, CTO Hospital, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
[6]Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Rome, Italy
[7]UniCamillus, Saint Camillus International University of Health Sciences, Rome, Italy

Abstract. – INTRODUCTION: Mononeuritis multiplex (MM) is an unusual form of peripheral neuropathy involving at least two noncontiguous peripheral nerve trunks. The pure sensory form of MM occurs rarely. Immunoglobulin (Ig)G subclass deficiency is a clinically and genetically heterogeneous disorder. Up to 50% of adults with selective subnormal IgG1 levels or selective IgG1 deficiency have a concomitant autoimmune disorder. Herein, we report the case of a patient with MM and selective IgG1 deficiency who showed remarkable clinical improvement after 2-year combination therapy with the DPP-4 inhibitor sitagliptin plus vitamin D3.

CASE REPORT: A 49-year-old man developed numbness in right hand and forearm. After 6 months, the patient developed left forefoot numbness. Approximately 8 years later, the patient started to develop numbness also in the right forefoot, along with symptoms of evening fatigue and occasional orthostatic hypotension. The patient also reported recurrent candidiasis in glans and intergluteal areas since adolescence. Electromyoneurography of lower and upper limbs revealed the presence of multiple mononeuropathies. Protein electrophoresis showed hypogammaglobulinemia and low serum IgG1 levels. Sural nerve biopsy showed the presence of perineuritis. The patient was diagnosed with MM due to perineuritis probably secondary to IgG1 deficiency. We, then, proposed combination therapy with sitagliptin and vitamin D3 in the attempt to achieve immunomodulation. At the last follow-up visit (2 years), the patient showed persistent clinical improvement, increase in IgG1 levels and normalization of protein electrophoresis.

CONCLUSIONS: To the best of our knowledge, this is the first case showing a remarkable clinical improvement of MM and selective IgG1 deficiency achieved through a combination therapy with sitagliptin and vitamin D3.

Key Words:
Mononeuritis multiplex, Mononeuropathy multiplex, Selective IgG1 deficiency, DPP-4 inhibitors, Sitagliptin, Vitamin D, Vitamin D3, Cholecalciferol, Hypovitaminosis D.

Introduction

Mononeuritis multiplex (MM), also known as mononeuropathy multiplex, is an unusual form of peripheral neuropathy, which consists of a painful, asymmetrical, asynchronous sensory and motor neuropathy afflicting at least two non contiguous peripheral nerve trunks[1]. The disease can affect multiple peripheral nerves in random areas of the body. Although MM is necessarily a sensory neuropathy[2], the pure sensory form of MM occurs rarely.

The electrophysiological diagnosis of MM requires a side-to-side asymmetry (greater than 50%) in the amplitudes of motor and somatosensory evoked potentials of two or more peripheral nerves. The nerve conduction velocity must be at least 75% lower than the normal values or no more than 25% above the upper limit of the normal

Corresponding Author: Marcelo Maia Pinheiro, MD; e-mail: marcelo.pinheiro@univag.edu.br

range[3-6]. MM is typically associated with various underlying systemic disorders, including vasculitis (either systemic or isolated to the nerves), diabetes mellitus, amyloidosis, inflammatory rheumatic diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus), infectious diseases, malignancies, paraneoplastic syndromes[7-10]. In some instances, perineuritis can present with clinical patterns of MM[11,12]. In cutaneous nerve and sural nerve biopsies, the perineuritis appears as a marked thickening of the perineurium surrounded by a mononuclear cell infiltrate and associated with axonal degeneration and/or prominent axon loss, which is particularly evident at the level of large and small myelinated fibers[13].

Other causes of neuropathy must be excluded to establish the diagnosis of MM, such as infection caused by acid-fast bacilli or interstitial immunoglobulin (Ig), complement, albumin or amyloid deposition[14,15]. Bourque et al[16] observed the presence of focal immunoglobulin G (IgG) and IgM deposits in the perineurium of the sural nerve from a patient with sensorimotor perineuritis, thus suggesting an autoimmune origin of the disease.

Antibody deficiency disorders may be idiopathic or may occur due to several causes, such as T-lymphocyte inability to signal B-lymphocytes or genetic defects in B-cell development resulting in immature B cells that are unable to proliferate into mature Ig-producing B cells[17]. Deficiency of one of the IgG subclasses is a clinically and genetically heterogeneous disorder characterized by frequent or severe bacterial infections of the upper and lower respiratory tract[18-21]. Up to 50% of adults with selective subnormal IgG1 levels or selective IgG1 deficiency may have concomitant autoimmune diseases[22,23]. IgG1 deficiency is usually associated with hypogammaglobulinemia because IgG1 antibodies constitue about 70% of the total serum IgG pool. Therefore, most of the patients with IgG1 deficiency will be classified as patients affected by common variable immunodeficiency (CVID) if IgA levels or IgM levels (or both) are also reduced. IgG1 deficiency is considerably more frequent in adults than children[24].

Dipeptidyl peptidase 4 (DPP-4) inhibitors (which are used as oral hypoglycemic agents for the treatment of type 2 diabetes) and vitamin D3 (cholecalciferol) have both been shown to exert anti-inflammatory and immunomodulatory effects *in vitro*[25,26], as well as in different autoimmune diseases like type 1 diabetes mellitus, autoimmune encephalomyelitis and multiple sclerosis *in vivo* and in clinical settings[27-29]. Our group has recently published a review article on the possible synergistic immunomodulatory effects exerted by a combination therapy based on DPP-4 inhibitors plus vitamin D3, which may have a remarkable therapeutic potential in autoimmune diabetes[30]. DPP-4, also known as CD26, is a serine exopeptidase expressed as a cell surface antigen (DPP-4/CD26) on several immune cells including T and B-lymphocytes, macrophages, and natural killer cells and appears to have an important role in the activation and differentiation of these cells[31].

Herein, we report the case of a patient with MM and selective IgG1 deficiency who experienced remarkable clinical improvement after 2-year combination therapy with the DPP-4 inhibitor sitagliptin plus vitamin D3.

Case Report

A 49-year-old man developed numbness in right hand and forearm in May 2008. The numbness was more pronounced in thumb, second finger, and third finger. After 6 months, he also developed left forefoot numbness, which was more pronounced in the toes. The patient did not report pain or muscle weakness. Physical examination and laboratory tests excluded the presence of diabetes, viral infections or autoimmune and rheumatic diseases. The patient had previously undergone electromyography, but the results were not available in this time. The symptoms remained stable until July 2016, when the man started to develop numbness even in the right forefoot. During the same period, the patient also experienced evening fatigue and occasional orthostatic hypotension. He also complained of sporadic electric-shock-like pain episodes in the same areas affected by numbness, which lasted only a few seconds. Moreover, he reported that numbness, fatigue, and symptoms of orthostatic hypotension worsened substantially when he consumed alcoholic beverages. Additionally, he reported recurrent candidiasis in glans and intergluteal areas since adolescence. However, he did not report recurrent respiratory infections, erectile dysfunction or fecal incontinence. There was no family history of autoimmune diseases. His parents are first cousins and both are affected by hypertension. His father was diagnosed with type 2 diabetes mellitus 40 years ago and has been affected by diabetic peripheral and autonomic neuropathy for the past 20 years. The patient has one brother, one sister, and two children, who are healthy.

Physical examination revealed: body weight 96 kg, height 181 cm (body mass index 29.3 kg/m^2), blood pressure 110/70 mmHg, heart rate 96 bpm. Orthostatic hypotension was not observed during the physical examination. Neurological examination revealed the presence of hypoesthesia in the aforementioned areas. Nerve hypertrophy was not identified, and Tinel's sign could not be elicited from any nerve trunk percussion. Impairment of postural or vibration sense was not observed at any time. There were no signs of muscle atrophy or reduced muscle strength. Tendon reflexes were decreased and plantar reflex was normal bilaterally.

Electromyoneurography of lower and upper limbs revealed the presence of multiple mononeuropathies involving the sensory fibers of the right radial, median, and ulnar nerves, along with the sensory fibers of sural nerve and superficial fibular nerve bilaterally. Electrophysiological analysis of the left radial, median, and ulnar nerves was normal. No signs of impaired motor unit control were observed. Magnetic resonance imaging of the cervical and lumbar spine was normal. The patient refused to undergo lumbar puncture.

Laboratory tests revealed persistent mild leukopenia and decreased CD3$^+$ and CD8$^+$ T-cell counts (Table I). Percentage and absolute count of B-cells were 3,1% and 43/mm^3 (reference range: 6.3-20.8% and 110-618/mm^3, respectively). Serum vitamin B12 levels were 332 pg/mL (reference range: 211-991 pg/mL), blood glucose was 91 mg/dL, glycated hemoglobin (HbA1c) was 5.6% (37.7 mmol/mol), and serum 25-hydroxyvitamin D [25-(OH) D levels were 20.7 ng/mL (indicative of hypovitaminosis D; reference range: 30-100 ng/mL). Electrolyte levels and markers of renal, liver and thyroid function were within the normal range. Serological tests for HIV, HBV, HCV, syphilis and HTLV-I/II were negative. The erythrocyte sedimentation rate (ESR) was 2 mm/h and C-reactive protein (CRP) levels were 1.13 mg/L. Additional laboratory tests excluded the presence of antinuclear antibodies (ANA), rheumatoid factor, lupus anticoagulant, anticardiolipin IgG antibodies, anti-Ro/SSA and anti-La/SSB antibodies, anti-DNA, p-ANCA and c-ANCA antibodies, anti-beta-2 glycoprotein antibodies (IgG/IgM), antibodies to myelin-associated glycoprotein (IgG/IgM). Immunofixation electrophoresis was normal. Serum complement components C3 and C4, total complement activity (CH-100), aldolase and creatine phosphokinase (CPK) were within the normal range. Protein electrophoresis showed hypogammaglobulinemia (0.65 g/dL [percentage: 10.7%]; reference range: 0.66-1.5 g/dL [percentage: 11.1-18.8%]). IgG1 levels were below the normal range (2660 mg/L; reference range: 4050-10.110 mg/L) (Figure 1), while total IgG levels were at the lower limit of the normal range (554 mg/dL; reference range: 540-1822 mg/dL) and IgG2, IgG3, IgG4, IgA, IgM, and IgE values were normal (Table I). Serum albumin levels were normal and urinalysis did not show proteinuria or macro- and microalbuminuria. Therefore, protein-losing nephropathy was unlikely. Additional viral serologic testing showed the presence of IgG antibodies to rubella virus, *Toxoplasma gondii*, measles virus and *Streptococcus pneumoniae* serotypes 14 and 18c.

Table I. Complete blood count and serum levels of immunoglobulins and 25-hydroxivitamin D before and 2 years following the initiation of combination therapywith sitagliptin plus vitamin D3. Reference range is indicated in brackets.

Test	Before treatment	After 2-year treatment
IgG (540-1822 mg/dL)	554	784
IgA (63-484 mg/dL)	94	110
IgM (22-240 mg/dL)	52	78
IgG2 (1690-7860 mg/L)	2540	3050
IgG3 (110-850 mg/L)	226	337
IgG4 (30-2010 mg/L)	362	429
Leukocytes (3600-11,000 cells/mm3)	3300	4700
Lymphocytes (1000-4500 cells/mm3)	1089	1363
Neutrophils (1700-7800 cells/mm3)	1881	2820
Monocytes (100-1,000 cells/mm3)	231	329
CD3+ cells (849-1963 cells/µL)	551	627
CD4+ cells (410-1590 cells/µL)	429	488
CD8+ cells (190-1140 cells/µL)	92	120
25-hydroxyvitamin D (30-100 ng/mL)	20.7	70.6

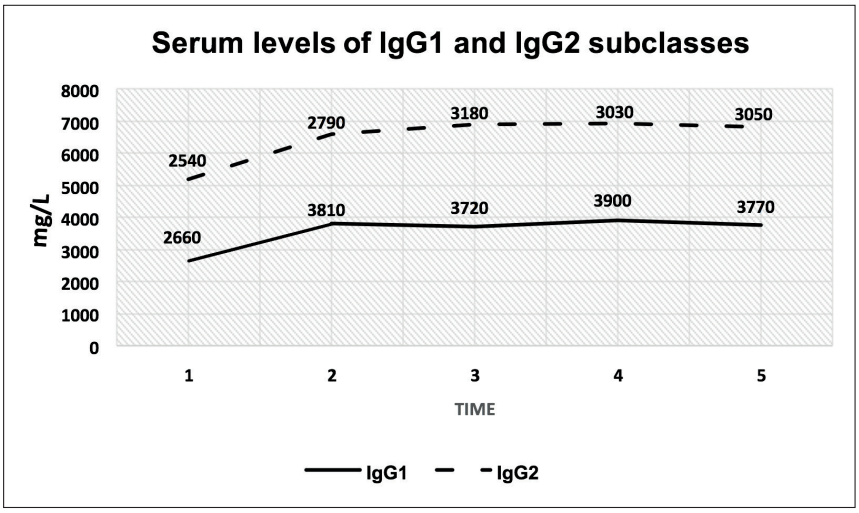

Figure 1. Serum levels of immunoglobulin (Ig)G1 and IgG2 subclasses before (time 1) and after (time 2 = 3 months, time 3 = 6 months, time 4 = 12 months, and time 5 = 24 months) the initation of combination therapy with sitagliptin plus vitamin D3.

The patient underwent: i) a skin biopsy, which was normal and did not show the presence of acid-fast bacilli, and ii) a biopsy of the left sural nerve, which showed nerve fascicles with fibrous thickening of the perineural tissue and reactive capillary proliferation. A mild lymphocytic infiltrate was observed in the vascular adventitia. Electron microscopy revealed the presence of a moderate to severe loss of myelinated nerve fibers, accompanied by irregularities in the myelin sheath with occasional tapering and some degree of axon regeneration. Nerve biopsy did not reveal the presence of acid-fast bacilli or abnormal deposits (Figure 2).

On the basis of these findings, the patient was diagnosed with MM due to perineuritis of autoimmune etiology, which was probably secondary to IgG1 deficiency. MM due to perineuritis is routinely treated with corticosteroids, while treatment of IgG1 deficiency (if indicated) consists of

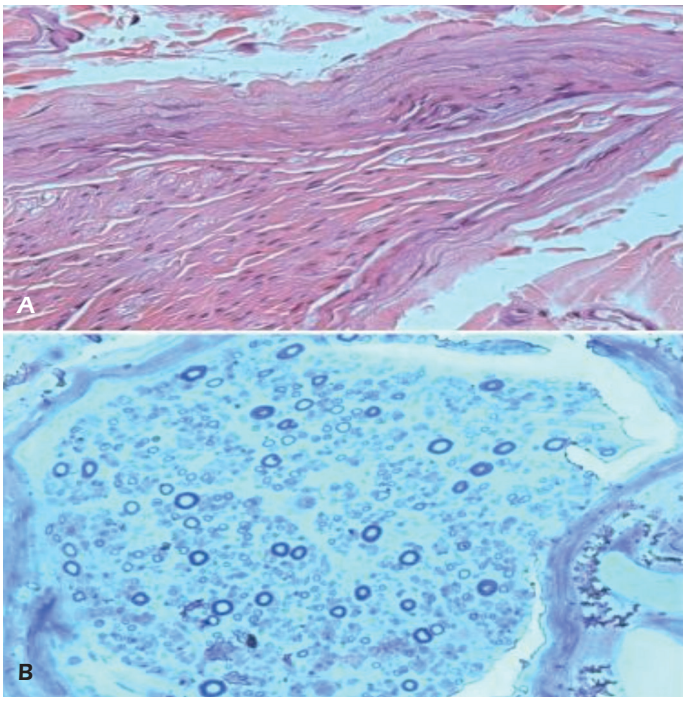

Figure 2. Sural nerve biopsy. **A**, Focal thickening of the perineurium with neovascularization (hematoxylin and eosin staining, x20 magnification). **B**, Nerve fascicle with moderate to severe loss of myelinated nerve fibers (toluidine blue staining, semithin section, x40 magnification).

intravenous immunoglobulin infusion. Although we proposed conventional treatment with corticosteroids, this was refused by the patient due to his family history of type 2 diabetes. We, then, proposed treatment with sitagliptin and vitamin D3 in the attempt to achieve immunomodulation. After having given and signed informed consent, the patient initiated a combination therapy with vitamin D3 (at a dose of 7,000 IU/day) plus sitagliptin at an initial dose of 300 mg/day for 1 month followed by a maintenance dose of 200 mg/day. The only self-limiting side effects reported by the patient were mild nausea and headache during the first week of treatment.

After 3 months, the patient showed remarkable clinical improvement. Fatigue and orthostatic hypotension disappeared, and the numbness markedly improved. Also, numbness was no longer exacerbated by consumption of alcoholic beverages. At the time of the publication of this case report (last follow-up visit: 2 years after treatment initiation), the patient was still on sitagliptin 200 mg/day plus vitamin D3 (5,000 IU/day), showing persistent clinical improvement, no hypoglycemia, stabilization of the electromyographic findings, increase in IgG1 levels (Figure 1), and normalization of protein electrophoresis and white blood cell count (Table I). Also, the patient did not report the occurrence of episodes of candidiasis following the treatment initiation. Complete blood count, markers of renal and liver function, as well as serum levels of amylase, calcium, phosphorus and parathyroid hormone (PTH) remained consistently normal throughout the follow-up period.

Discussion

Herein, we reported the first case of a pure sensory MM in a patient with selective IgG1 deficiency who responded positively to the immunomodulatory therapy with sitagliptin and vitamin D3. The findings observed in this case report are promising, considering the rare association between MM and selective IgG1 deficiency and the optimal clinical and immunological response observed following the initiation of the combination therapy. Furthermore, sitagliptin plus vitamin D3 combination therapy was well tolerated, even though we administered sitagliptin at a dose that was two-three times greater (200-300 mg/day) than the maximum recommended dose (100 mg/day) employed for the treatment of type 2 diabetes. In this regard, it is worth noting that previous studies[32,33] investigated the safety and efficacy of two different doses (100 mg and 200 mg/day) of once-daily oral sitagliptin adminsitered as monotherapy in patients with inadequately controlled type 2 diabetes. Although these studies did not find significant differences between the low-dose and the high-dose groups in terms of glucose-lowering efficacy of sitagliptin, both treatments showed a good short-term (up to 24 weeks) safety and tolerability profile[32,33]. In these studies[32,33], there was no statistically significant difference between placebo and sitagliptin (100 and 200 mg) groups in the incidence of serious or drug-related clinical adverse experiences, such as hypoglycaemia, abdominal pain, diarrhoea, náusea, vomiting, nasopharyngitis, back pain, osteoarthritis and pain in extremities. As it has been shown in preclinical studies[34], higher doses of sitagliptin and/or other DPP-4 inhibitors may be required to achieve immunomodulatory effects even in clinical settings.

Emerging evidence[35,36] suggests that both DPP-4 inhibitors and vitamin D exert pleiotropic effects beyond their well-known role in the regulation of glucose and bone homeostasis, respectively. Mahabadi-Ashtiyani et al[37] have recently shown that the combined use of sitagliptin and vitamin D3 in patients with type 2 diabetes significantly reduces the levels of IL-6 and TNF-α (produced by peripheral blood mononuclear cells) compared to sitagliptin or vitamin D3 used alone. The same combination therapy used in patients with type 2 diabetes has been shown to exert synergic anti-inflammatory effects on immune system through upregulation of FOXP3 and IL-37, along with downregulation of RORγt and BCL6 and reduced IFN-γ, IL-17 and IL-21 production[38].

We have recently suggested that the immunomodulatory effects of the combination therapy with sitagliptin plus vitamin D3 occur upon adminsitration of higher doses than those tested in previous clinical studies[30,39]. Additionally, our group and other authors showed that immunomodulatory effects of DPP-4 inhibitors occur in a dose-dependent manner, even in experimental autoimmune encephalomyelitis[25,28,40,41]. Higher doses of sitagliptin have been shown to increase plasma concentrations of glucagon-like peptide-1 (GLP-1) in humans[42]. Importantly, animal studies[43-45] have shown that GLP-1 is able to exert neuroprotective effects in central and peripheral nervous system. Also, a possible direct neuroprotective activity of sitagliptin *via* reduction of neuroinflammation (beyond the incretin effect)[46] could partly account for the beneficial effects obtained from its usein this case report. Interesting-

ly, experimental studies[47,48] showed that DPP-4 inhibitors can exert beneficial effects in diabetic peripheral neuropathy, reducing nerve fiber loss and counteracting the nerve conduction velocity deficit. In particular, sitagliptin (alone or in combination with metformin or amitriptyline) exerted neural protection and reversed the alteration of biochemical parameters in rats with streptozotocin-nicotinamide induced type 2 diabetes[49]. Recently, Shigematsu et al[50] demonstrated the *in vitro* and *in vivo* efficacy of the DPP-4 inhibitor alogliptin in preventing oxaliplatin-induced peripheral neuropathy.

Additionally, neuropeptide Y (NPY) one of the main substrates of DPP-4[51], has been shown to selectively mobilize "B1-like" B cells in a dose-dependent manner, thus suggesting the existence of a strict relationship between the effects of DPP-4 inhibition on nervous system and immune cells[51]. However, the increase in IgG1 levels observed in our patient cannot be explained by the known effects of DPP-4 inhibitors on immune system[30,52].

Bühling et al[53] investigating the functional role of DPP-4 on human B lymphocytes have demonstrated that, upon activation, up to 50% of B-cells express CD26/DPP-4. Selective suppression of DPP-4 activity reduces B-cell activation and synthesis of DNA in a dose-dependent manner[53]. Also, it has been demonstrated[54] that DPP-4/CD26 knockout mice (CD26[-/-] mice) show decreased immunoglobulin production. In addition, Yan et al[54] showed that immunization with pokeweed mitogen *in vivo* is associated with markedly lower serum levels of total IgG, IgG1, IgG2a, and IgE in CD26(-/-) mice compared to CD26(+/+) animals, while no difference was found in IgM production. These results indicate that CD26/DPP-4 contributes to the regulation of T cell-dependent antibody production and immunoglobulin isotype switching of B cells[54]. Another *in vivo* study conducted in rats investigated the long-term consequences of DPP-4 deficiency, showing that this deficiency resulted in markedly decreased numbers of B cells in later life[55]. Overall, these studies indicate that DPP-4 is involved in B-lymphocyte activation and modulation and are of critical importance to better elucidate the effects of DPP-4 and DPP-4 inhibition on signaling pathways related to B-lymphocyte development, activation and maturation.

DPP-4 can also modulate immune responsiveness by influencing cell adhesion, cell-cell communication, peptide transport, migration and chemotaxis of immune cells[56]. In addition to its immunomodulatory function, DPP-4 is a serine exopeptidase that binds to fibronectin and can inactivate specific chemokines, incretin hormones and neuropeptides[55,56]. Vitamin D has been shown to exert anti-inflammatory and immunomodulatory effects by acting on antigen-presenting cells, T-lymphocytes and B lymphocytes[30,36,57]. As previously mentioned, the increase in IgG1 levels observed in our patient cannot be explained by the known mechanisms of vitamin D3 on the immune system. In fact, 1,25(OH)2D3 (also referred to as calcitriol, which is the active form of vitamin D) inhibits differentiation of B cells to plasma cells and immunoglobulin production[57], which is the opposite effect compared to that observed in our case.

A possible explanation for theses results relies on the fact that combination therapy with sitagliptin and vitamin D3 may regulate T-cell function and cytokine abnormalities, and enhance the interaction between $CD4^+$ T cells and B cells, thus leading to more efficient B-cell activation and antibody production. DPP-4 inhibition with sitagliptin in combination with vitamin D3 increased the serum levels of immunoglobulins and restored the class switching to IgG1, probably by partly reversing a likely defect in lymphocyte migration to the proper microenvironment, where B cells proliferate and differentiate into immunoglobulin-producing cells. Finally, this study indicates that the pharmacological inhibition of DPP-4 activity in combination with vitamin D3 supplementation may indirectly modulate stress-induced B-cell redistribution[58] and composition of B cell reservoirs, resulting in improved maturation and activation of immunoglobulin-producing cells and immunoglobulin production.

Moreover, our patient did not report episodes of candidiasis following the initiation of combination therapy with sitagliptin and vitamin D3, further suggesting beneficial effects of this therapy on immune function. Genitourinary tract infections represent the most common adverse event related to the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors, which are a new class of anti-hyperglycemic agents. Of note, combination therapy with DDP-4 inhibitors has been shown to reduce the risk of genitourinary tract infections associated with SGLT2 inhibitors[59]. Therefore, DPP-4 ihibitors may play a beneficial role in the prevention of genitourinary fungal infections.

Although we did not perform specific tests to assess cell-mediated immunity in our patient, $CD8^+$ T cell count remained below the normal range and normalization of total white blood cell count also occurred. In adults, selective deficien-

cy of IgG1 is characterized by low serum levels of IgG1, hypogammaglobulinemia and normal levels of other IgG subclasses, IgA, and IgM; this disease can cause recurrent candidiasis of the skin, mouth, glans, and vulvovaginal area[22]. Our patient met diagnostic criteria for selective IgG1 deficiency. Of note, Lacombe et al[22] documented that only 16,8% of a cohort of 119 patients with selective IgG1 deficiency did not report infections; 2.5% of patients reported candidiasis, and 19 patients (15.9%) displayed concomitant autoimmune diseases. These results further confirm our patient diagnosis. The parallel increase in serum levels of IgG1 and IgG2 observed in our patient (Figure 1) strengthens the hypothesis that sitagliptin and vitamin D3 combination therapy may have played a role in improving immunoglobulin production and isotype switching. Despite the low B-cell count observed in our patient, detectable levels of IgG antibodies against rubella virus, *Toxoplasma gondii*, measles virus and *Streptococcus pneumoniae* serotypes 14 and 18c suggest normal B-cell function and potentially account for the absence of respiratory infections.

Conclusions

To the best of our knowledge, this is the first case showing the safety and efficacy of sitagliptin and vitamin D3 combination therapy in MM associated with selective IgG1 deficiency. Of note, 2-year combination therapy with sitagliptin and vitamin D3 markedly improved symptoms related to perineuritis and increased serum levels of IgG1. This therapy was safe and well tolerated, even if the administered sitagliptin dose was greater than that commonly used to treat type 2 diabetes. Importantly, safety of the same sitagliptin dose has been previously shown[32,33] also in patients with type 2 diabetes. Future clinical studies are therefore needed to further investigate the safety and efficacy of the combination therapy with sitagliptin and vitamin D3 in MM, autoimmune diseases and immunodeficiency disorders. Further mechanistic investigation to better elucidate the exact mechanisms of action of sitagliptin and vitamin D3 combination therapy in immune system is also warranted.

Acknowledgments

We are grateful to Luciano Foroni, MD, Ph.D. (São Paulo University) and Angelina Maria Martins Lino, MD, Ph.D. (São Paulo University) for the sural nerve biopsies.

Author Contributions

All authors drafted, reviewed and approved the final version of the article. Ludmilla Luzia Pires Amaral Resende, MD (allergist and immunologist) and Marcelo Maia Pinheiro, MD (endocrinologist) are following
the patient.

Availability of Data and Materials

All exams and biopsies are available for analysis, safeguarding patient confidentiality.

Ethical Approval and Informed Consent

Written informed consent was obtained from the patient to start the treatment.

Consent for Publication

Consent for publication was obtained from the patient.

Conflict of Interests

The authors declare that they have no conflict of interest to disclose.

References

1) Zhang YS, Sun AP, Chen L, Dong RF, Zhong YF, Zhang J. Nerve biopsy findings contribute to diagnosis of multiple mononeuropathy: 78% of findings support clinical diagnosis. Neural Regen Res 2015; 10: 112-118.
2) Birnbaum J. The nervous system in rheumatic disease. In Rheumatology: Sixth Edition. Elsevier Inc, 2014: 298-305.
3) Ross MA. Electrodiagnosis of peripheral neuropathy. Neurol Clin 2012; 30: 529–549.
4) Bromberg MB. An electrodiagnostic approach to the evaluation of peripheral neuropathies. Phys Med Rehabil Clin N Am 2013; 24: 153-168.
5) Levine TD, Saperstein DS. Laboratory evaluation of peripheral neuropathy. Neurol Clin 2013; 31: 363-376.
6) Chung T, Prasad K, Lloyd TE. Peripheral neuropathy: clinical and electrophysiological considerations. Neuroimag Clin N Am 2014; 24: 49-65.
7) Sheikh AAE., Abu Baker Sheikh UT, Siddiqui FS, Malik WT, Rajput HM, Ahmad I. Paraneoplastic mononeuritis multiplex: a unique presentation of non-hodgkin lymphoma. Cureus 2018; 10: 1-8.
8) Xie F, Creamer D. Neuropathy and a rash. BMJ 2017; 359: 1-2.
9) Mohd R, Nordin FZ, Cader R. Chronic inflammatory demyelinating polyneuropathy in systemic lupus erythematosus: a rare entity. Open Med J 2018; 5: 56-61.
10) Agarwal V, Singh R, Chauhan S, Tahlan A, Ahuja CK, Goel D, Pal L. A clinical, electrophysiological, and pathological study of neuropathy in rheumatoid arthritis. Clin Rheumatol 2008; 27: 841-844.

11) Sorenson EJ, Sima AA, Blaivas M, Sawchuk K, Wald JJ. Clinical features of perineuritis. Muscle Nerve 1997; 20: 1153-1157.
12) Simmons Z, Albers JW, Sima AA. Case-of-the-month: perineuritis presenting as mononeuritis multiplex. Muscle Nerve 1992; 15: 630-635.
13) Zhang YS, Sun AP, Chen L, Dong RF, Zhong YF, Zhang J. Nerve biopsy findings contribute to diagnosis of multiple mononeuropathy: 78% of findings support clinical diagnosis. Neural Regen Res 2015; 10: 112-118.
14) Asbury AK, Picard EH, Baringer JR. Sensory perineuritis. Arch Neurol 1972; 26: 302-312.
15) Matthews WB, Squier MV. Sensory perineuritis. J Neurol Neurosurg Psychiatry 1988; 51: 473-475.
16) Bourque CN, Anderson BA, del Campo CM, Sima AA. Sensorimotor perineuritis–an autoimmune disease?. Can J Neurol Sci 1985; 12: 129-133.
17) Justiz Vaillant AA, Ramphul K. Antibody Deficiency Disorder. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507905/.
18) Herrod HG. Clinical significance of IgG subclasses. Curr Opin Pediatr 1993; 5: 696-699.
19) Buckley RH. Immunoglobulin G subclass deficiency: fact or fancy? Curr Allergy Asthma Rep 2002; 2: 356-360.
20) Aghamohammadi A, Plebani A, Lougaris V, Durandy A, Condino-Neto A, Kanegane H, Hammarström L. Predominantly antibody deficiencies. In Primary Immunodeficiency Diseases. Springer, Berlin, Heidelberg, 2017: 183-244.
21) Cinetto F, Scarpa R, Pulvirenti F, Quinti I, Agostini C, Milito C. Appropriate lung management in patients with primary antibody deficiencies. Expert Rev Respir Med 2019; 13: 823-838.
22) Lacombe C, Aucouturier P, Preud'homme JL. Selective IgG1 deficiency. Clin Immunol Immunopathol 1997; 84: 194-201.
23) Barton JC, Bertoli LF, Barton JC, Acton RT. Selective subnormal IgG1 in 54 adult index patients with frequent or severe bacterial respiratory tract infections. J Immunol Res 2016; 2016: 1-10.
24) van der Burg M, Weemaes CM, Cunningham-Rundles C. Isotype Defects. In Stiehm's Immune Deficiencies 2014: 389-408. Academic Press.
25) Pinheiro MM, Stoppa CL, Valduga CJ, Okuyama CE, Gorjão R, Pereira R. MS, Diniz SN. Sitagliptin inhibit human lymphocytes proliferation and Th1/Th17 differentiation in vitro. Eur J Pharm Sci 2017; 100: 17-24.
26) Shirazi HA, Rasouli J, Ciric B, Wei D, Rostami A, Zhang GX. 1, 25-Dihydroxyvitamin D3 suppressed experimental autoimmune encephalomyelitis through both immunomodulation and oligodendrocyte maturation. Exp Mol Pathol 2017; 102: 515-521.
27) Pinheiro MM, Pinheiro FMM; Torres M. Four-year clinical remission of type 1 diabetes mellitus in two patients treated with sitagliptin and vitamin D3. Endocrinol Diabetes Metab Case Rep 2016; 2016: 1-6.
28) Steinbrecher A, Reinhold D, Quigley L, Gado A, Tresser N, Izikson L, Ansorge S. Targeting dipeptidyl peptidase IV (CD26) suppresses autoimmune encephalomyelitis and up-regulates TGF-β1 secretion in vivo. J Immunol 2001; 166: 2041-2048.
29) Hupperts R, Smolders J, Vieth R, Holmøy T, Marhardt K, Schluep M, Killestein J, Barkhof F, Grimaldi LM, Beelke M. High dose cholecalciferol (vitamin D3) oil as add-on therapy in subjects with relapsing-remitting multiple sclerosis (RRMS) receiving subcutaneous interferon β-1a (scIFNβ-1a). Neurology 2017; 88: S44.005.
30) Pinheiro MM, Pinheiro FMM, Trabachin ML. Dipeptidyl peptidase-4 inhibitors (DPP-4i) combined with vitamin D3: An exploration to treat new-onset type 1 diabetes mellitus and latent autoimmune diabetes in adults in the future. Int Immunopharmacol 2018; 57: 11-17.
31) Ohnuma K, Dang NH, Morimoto C. Revisiting an old acquaintance: CD26 and its molecular mechanisms in T cell function. Trends immunol 2008; 29: 295-301.
32) Raz I, Hanefeld M, Xu L, Caria C, Williams-Herman D, Khatami H. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. Diabetologia 2006; 49: 2564-2571.
33) Aschner P, Kipnes MS, Lunceford JK, Sanchez M, Mickel C, Williams-Herman DE. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care 2006; 29: 2632-2637.
34) Yang L, Yuan J, Zhou Z. Emerging roles of dipeptidyl peptidase 4 inhibitors: anti-inflammatory and immunomodulatory effect and its application in diabetes mellitus. Can J Diabetes 2014; 38: 473-479.
35) Aroor AR, Sowers JR, Jia G, DeMarco VG. Pleiotropic effects of the dipeptidylpeptidase-4 inhibitors on the cardiovascular system. Am J Physiol Heart Circ Physiol 2014; 307: H477-H492.
36) Caprio M, Infante M, Calanchini M, Mammi C, Fabbri A. Vitamin D: not just the bone. Evidence for beneficial pleiotropic extraskeletal effects. Eat Weight Disord 2017; 22: 27-41
37) Mahabadi-Ashtiyani E, Sheikh V, Borzouei S, Salehi I, Alahgholi-Hajibehzad M. Effect of sitagliptin and vitamin d3 on secretion of IL-6 and TNF-α inflammatory factors in patients with type 2 diabetes. Avicenna J Clin Med 2018; 25: 134-141
38) Telikani Z, Sheikh V, Zamani A, Borzouei S, Salehi I, Amirzargar MA, Alahgholi-Hajibehzad M. Effects of sitagliptin and vitamin D3 on T helper cell transcription factors and cytokine production in clinical subgroups of type 2 diabetes mellitus: highlights upregulation of FOXP3 and IL-37. Immunopharmacol Immunotoxicol 2019; 41: 299-311.
39) Pinheiro M, Pinheiro F. Prolonging the honeymoon phase in T1DM with sitagliptin plus vitamin D3. Diabetes Technol Ther. Mary Ann Liebert, Inc 2020; 22: A26-A26.
40) Flentke GR, Munoz E, Huber BT, Plaut AG, Kettner CA, Bachovchin WW. Inhibition of dipeptidyl aminopeptidase IV (DP-IV) by Xaa-boroPro dipeptides and use of these inhibitors to examine the role of DP-IV in T-cell function. Proc Natl Acad Sci U S A 1991; 88: 1556-1559.
41) Reinhold D, Bank U, Bühling F, Täger M, Born I, Faust J, Ansorge S. Inhibitors of dipeptidyl peptidase IV (DP IV, CD26) induces secretion of transforming growth factor-β1 (TGF-β1) in stimulated mouse splenocytes and thymocytes. Immunol Lett 1997; 58: 29-35.

42) Bergman AJ, Stevens C, Zhou Y, Yi B, Laethem M, De Smet M, Tanen M. Pharmacokinetic and pharmacodynamic properties of multiple oral doses of sitagliptin, a dipeptidyl peptidase-IV inhibitor: a double-blind, randomized, placebo-controlled study in healthy male volunteers. Clin Ther 2006; 28: 55-72.
43) Li Y, Perry T, Kindy MS, Harvey BK, Tweedie D, Holloway HW, Brossi A. GLP-1 receptor stimulation preserves primary cortical and dopaminergic neurons in cellular and rodent models of stroke and Parkinsonism. Proc Natl Acad Sci U S A 2009; 106: 1285-1290.
44) Perry T, Holloway HW, Weerasuriya A, Mouton PR, Duffy K, Mattison JA, Greig NH. Evidence of GLP-1-mediated neuroprotection in an animal model of pyridoxine-induced peripheral sensory neuropathy. Exp Neurol 2007; 203: 293-301.
45) Holscher C. Central effects of GLP-1: new opportunities for treatments of neurodegenerative diseases. J Endocrinol 2013; 221: 31-41.
46) Wiciński M, Wódkiewicz E, Słupski M, Walczak M, Socha M, Malinowski B, Pawlak-Osińska K. Neuroprotective Activity of Sitagliptin via Reduction of Neuroinflammation beyond the Incretin Effect: Focus on Alzheimer's Disease. Biomed Res Int 2018; 2018: 1-9.
47) Jin HY, Liu WJ, Park JH, Baek HS, Park TS. Effect of dipeptidyl peptidase-IV (DPP-IV) inhibitor (Vildagliptin) on peripheral nerves in streptozotocin-induced diabetic rats. Arch Med Res 2009; 40: 536-544.
48) Bianchi R, Cervellini I, Porretta-Serapiglia C, Oggioni N, Burkey B, Ghezzi, P, Lauria G. Beneficial effects of PKF275-055, a novel, selective, orally bioavailable, long-acting dipeptidyl peptidase IV inhibitor in streptozotocin-induced diabetic peripheral neuropathy. J Pharmacol Exp Ther 2012; 340: 64-72.
49) Sharma AK, Sharma A, Kumari R, Kishore K, Sharma D, Srinivasan BP, Sharma P. Sitagliptin, sitagliptin and metformin, or sitagliptin and amitriptyline attenuate streptozotocin-nicotinamide induced diabetic neuropathy in rats. J Biomed Res 2012; 26: 200-210.
50) Shigematsu N, Kawashiri T, Kobayashi D, Shimizu S, Mine K, Hiromoto S, Shimazoe T. Neuroprotective effect of alogliptin on oxaliplatin-induced peripheral neuropathy in vivo and in vitro. Sci Rep 2020; 10: 1-8.
51) Bedoui S, Kuhlmann S, Nave H, Drube J, Pabst R, von Hörsten S. Differential effects of neuropeptide Y (NPY) on leukocyte subsets in the blood: mobilization of B-1-like B-lymphocytes and activated monocytes. J Neuroimmunol 2001; 117: 125-132.
52) Zhao Y, Yang L, Wang X, Zhou Z. The New insights from DPP-4 inhibitors: their potential immune modulatory function in autoimmune diabetes. Diabetes Metab Res Rev 2014; 30: 646-653.
53) Bühling F, Junker U, Reinhold D, Neubert K, Jäger L, Ansorge S. Functional role of CD26 on human B lymphocytes. Immunol Lett 1995; 45: 47-51.
54) Yan S, Marguet D, Dobers J, Reutter W, Fan H. Deficiency of CD26 results in a change of cytokine and immunoglobulin secretion after stimulation by pokeweed mitogen. Eur J Immunol 2003; 33: 1519-1527.
55) Klemann C, Schade J, Pabst R, Leitner S, Stiller J, Von Hörsten S, Stephan M. CD26/dipeptidyl peptidase 4-deficiency alters thymic emigration patterns and leukocyte subsets in F344-rats age-dependently. Clin Exp Immunol 2009; 155: 357-365.
56) Klemann C, Wagner L, Stephan M, von Hörsten S. Cut to the chase: a review of CD26/dipeptidyl peptidase-4's (DPP4) entanglement in the immune system. Clin Exp Immunol 2016; 185: 1-21.
57) Chen S, Sims GP, Chen XX, Gu YY, Chen S, Lipsky PE. Modulatory effects of 1, 25-dihydroxyvitamin D3 on human B cell differentiation. J Immunol 2007; 179: 1634-1647.
58) Dhabhar FS, Malarkey WB, Neri E, McEwen BS. Stress-induced redistribution of immune cells–From barracks to boulevards to battlefields: a tale of three hormones--Curt Richter Award Winner. Psychoneuroendocrinology 2012; 37: 1345-1368.
59) Fadini GP, Bonora BM, Mayur S, Rigato M, Avogaro A. Dipeptidyl peptidase-4 inhibitors moderate the risk of genitourinary tract infections associated with sodium-glucose co-transporter-2 inhibitors. Diabetes Obes Metab 2018; 20: 740-744.