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SPECIAL ARTICLE

Giant cell arteritis and polymyalgia rheumatica after influenza vaccination: report of 10 cases and review of the literature

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Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are inflammatory rheumatic diseases common in people over the age of 50 years. Herein, we report 10 cases of previously healthy subjects who developed GCA/PMR within 3 months of influenza vaccination (Inf-V). A Medline search uncovered additional 11 isolated cases of GCA/PMR occurring after Inf-V. We discuss the role of individual susceptibility, the potential function of immune adjuvants as triggers of autoimmunity post-vaccination, and the correlation of our observation with the 'ASIA' syndrome, i.e. autoimmune/inflammatory syndrome induced by adjuvants and including post-vaccination phenomena. *Lupus* (2012) **21,** 153–157.

Key words: giant cell arteritis; polymyalgia rheumatica; influenza vaccination; 'ASIA' syndrome

Introduction

Giant cell (temporal) arteritis (GCA), also known as Horton's disease is a segmental giant cell vasculitis, with a distinct tropism for large and medium-size elastic arteries. GCA is common in older age groups, and the average age of onset is the sixth to seventh decade of life.[1] GCA is often associated with polymyalgia rheumatica (PMR). The latter is an inflammatory rheumatic disease, which also presents commonly in people over the age of 50 years and is characterized by pain and morning stiffness in the shoulder and pelvic girdles, alongside evidence of an underlying inflammatory reaction. PMR may develop without GCA.[2] A survey of familial aggregation of GCA and PMR points to a genetic predisposition, whereas environmental factors, possibly viral, could trigger disease onset in up to one-fourth of cases.[3,4]

In 2005 we recorded a female patient showing the first symptoms of GCA 20 days following influenza vaccination (Inf-V). Thereafter we identified 10 patients who developed GCA/PMR within 3 months of Inf-V.

Since another 11 isolated cases of GCA/PMR occurring after Inf-V have been reported in the medical literature, we can hypothesize that GCA/PMR following influenza vaccination is not as rare as previously believed. Additionally we discuss herein the genetic susceptibility as well as the role of adjuvants in the so-called 'ASIA' syndrome.[5]

Patients and methods

Between 1978 and 2005 in our clinical autoimmunity unit, 73 patients were diagnosed with GCA confirmed by biopsy, and 22 with PMR. In all GCA patients, the diagnosis was established according to the 1990 American College of Rheumatology, with PMR diagnosis according to the 1984 Healey criteria. In this cohort of 95 GCA/PMR patients, 48/73(68%) of GCA and 15/22 (65%) of PMR patients presented with a preliminary diagnosis of fever of unknown origin (FUO). In 2005 we noticed that one female patient diagnosed with GCA had undergone influenza vaccination 20 days before the beginning of her symptoms.

This occasional observation prompted us systematically thereafter to search for data on

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Table 1 Cases of GCA/PMR following INF-V admitted to the Clinical Autoimmunity Unit (2005–2010)

Observational period (2005–2010) Patient #	*Sex, age (years)*[a]	*Disease*	*Type of vaccination*	*Time interval*[b]	*HLA typing*
1	F, 80	GCA/PMR*	INF-V	3 months	NA
2	F, 64	PMR	INF-V	1 month	A2, A31, B8, B51, Cw7 DR11, DR15, DQ1, DQ7
3	F, 78	GCA/PMR*	INF-V	3 weeks	NA
4	F, 67	GCA*	INF-V	1 month	NA
5	F, 78	GCA*	INF-V	2 months	NA
6	F, 71	PMR PMR Relapse	INF-V INF-V (2 years later)	2 months 2 weeks	NA
7	F, 80	GCA*	INF-V	2 months	A24, A30, B39, B45, Bw4, Bw6, Cw6, Cw7, DR4, DR8, DR53, DQ4, DQ8
8	F, 73	GCA*	INF-V	3 months	NA
9	F, 70	GCA*	INF-V	3 months	NA
10	F, 74	GCA*	INF-V	1 months	NA

[a]At the time of onset of disease. [b]Time interval between vaccine administration and onset of disease. *Diagnosis confirmed by biopsy. GCA, giant cell arteritis; PMR, polymyalgia rheumatica; NA, not available.

influenza vaccination, before the onset of symptoms, among all patients diagnosed with GCA/PMR. Over the following 6 years (2005–2010) we identified 10 patients who developed GCA/PMR within 3 months of receiving Inf-V.

For comparison, we conducted a systematic literature survey of reports on GCA/PMR occurring after Inf-V. We also collected and analysed data on gender, age at disease onset, features of the disease and type of vaccination in these reported cases. We utilized a PubMed/Medline search without any date limitations, mainly using the search terms 'polymyalgia rheumatica (medical subject headings [MeSH])' and 'giant cell arteritis (MeSH)' relating to the terms 'influenza vaccination (MeSH)'. The search included mostly English language papers, although articles of exceptional relevance written in other languages were also assessed. We compared the data accumulated from our literature review with our cases of post-Inf-V GCA/PMR diagnosed between 2005 and 2010.

Results

Over the 6-year period (2005–2010) 20 patients were given a diagnosis of GCA/PMR at our centre, of whom 10/20 (50%) had received an influenza vaccination 20 days to 3 months before the beginning of the disease (Table 1). Among this group of patients, 8 had been given a diagnosis of GCA confirmed by biopsy, and 2 PMR. Patients #1 and #3 (Table 1) were suffering concomitantly from GCA and PMR. Interestingly, all patients were female and previously healthy. Patients' age at the time of the diagnosis ranged between 64 and 80 years, with a median of 73.5. All temporal artery biopsies confirmed the diagnosis of GCA. HLA typing was evaluated in two patients (Table 1). All patients received steroid therapy for at least 24 months, with full clinical remission. Of note, patient #6 diagnosed with PMR following Inf-V was in clinical remission subsequent to steroid therapy when a relapse of her disease occurred 2 years later, following revaccination with seasonal Inf-V.

Our literature survey yielded 7 isolated cases of PMR and 4 of GCA following Inf-V (Table 2). The first case was described in 1976 and the last in 2008; 6 patients were male and 5 female, and their median age was 72 years. Another case of GCA following Inf-V was published while this manuscript was under review.[6] The interval between vaccine administration and the onset of clinical manifestations ranged from a minimum of 1 day to a maximum of 3 weeks. HLA typing revealed the presence of alleles at the DRB1 locus, particularly the HLA-DRB1*04 variants. Among patients with GCA, 3 developed the disease after Inf-V,[7,8,9] being previously healthy subjects, whereas 1 occurred 6 months after administration of hepatitis B vaccine in a woman in remission after a diagnosis of PMR 2 years previously.[10] One year after the clinical remission of PMR and 3 days after receiving Inf-V,

Table 2 Clinical findings of cases reported in the literature of GCA and PMR following influenza vaccination (INF-V); HLA typing is recorded where available

Case reference	*Sex, age (years)*[a]	*Disease*	*Type of vaccination*	*Time interval*[b]	*HLA typing*
Ghose et al.[7]	F, 76	GCA	INF-V	1 week	NA
Gerth[12]	F, 67	PMR relapse	INF-V	2–3 weeks	NA
Brown and Bertouch[13]	M, 65	PMR	INF-V 'Fluvax® 92'	3 weeks	NA
Perez[14]	M, 61	PMR	INF-V 'Inflexal Berna® 1998-99'	2 weeks	DRB1*0404
Liozon et al.[16]	F, 91	PMR	INF-V 'Fluarix®'	1 day	NA
Perez[8]	M, 76	GCA	INF-V	1 week	A1, A11, B27, B51, Bw4 DRB1*01 DRB1*04
Saadoun et al.[10]	F, 64	PMR/GCA	INF-V	3 days	NA
Saadoun et al.[10]	F, 68	PMR	Tetanus vaccination	Few days later	NA
Finsterer et al.[11]	M, 70	GCA	INF-V	Few days later	NA
Marti and Anton[15]	M, 79	PMR	INF-V 'Evagrip'	2 days	DRB1*0401
Pou et al.[9]	M, 74	GCA	INF-V	1 week	NA

[a]At the time of onset of disease. [b]Time interval between vaccine administration and onset of disease. GCA, giant cell arteritis; PMR, polymyalgia rheumatica; NA, not available.

temporal migraine and a dry cough appeared, suggesting a diagnosis of GCA. Finsterer and colleagues[11] described the case of a 70-year-old male patient who was vaccinated against influenza despite the onset of a common cold 5 days previously. Although it could not be excluded that the 'influenza-like' symptoms at onset were the initial manifestation of GCA, after receiving Inf-V the patient's clinical condition worsened and a cavernous sinus thrombosis was diagnosed, complicating GCA. Saadoun et al.[10] also described the case of a 68-year-old female patient with a previous diagnosis of PMR, clinically recovered after steroid therapy, who had a relapse of the disease 4 years later when she underwent tetanus vaccination. Gerth[12] described a similar case of a woman who had a PMR relapse some weeks after receiving Inf-V and 7 years after the first diagnosis of PMR, already in remission. All other patients diagnosed with PMR following administration of Inf-V were previously healthy.[13–16]

Discussion

Immunization with influenza vaccine is a widely accepted recommendation and a common practice in elderly and high-risk individuals, as it is highly effective and well tolerated. Mild transitory side effects after vaccination are common, while systemic complications such as vasculitis and rheumatic disorders remain rare.[15] Autoimmune complications, such as the high incidence of Guillain-Barré syndrome following the swine-flu vaccination programme in North America in 1976–1977, have been reported.[17]

In the current study our cohort of patients, as well as the literature referenced below, further support the possibility of Inf-V triggering GCA/PMR in healthy subjects, or those at risk for developing these diseases, with a latency period of up to 3 months.

In our case series observed between 2005 and 2010, 20 patients were affected by GCA/PMR of whom 10 were diagnosed following administration of Inf-V, with a median of 2 post-immunization cases/year and a frequency of 1/2 cases (50%). This vaccination frequency level is 15% less than that predicted by the Italian Health Ministry, which for Inf-V has a target of coverage of 60–65% in people over 65 years with one risk factor.[18] Although this analysis has been performed on only a small number of cases, we suggest that both environmental/vaccine and genetic factors play a role in the pathogenesis of these diseases. Indeed, genetic linkage studies have demonstrated an association of GCA and PMR with alleles at the HLA-DRB1 locus,[19] so we could speculate that these factors, similarly, could predispose to the development of GCA/PMR following administration of Inf-V.

Combining the analysis of the literature and our case series of rheumatic disorders related to Inf-V, a period of over 30 years is encompassed, and therefore we suggest that this phenomenon is not correlated with the viral specificity of the vaccine. Indeed, the viral components included in vaccines vary from year to year, on the basis of the expected type of influenza virus, whereas a restricted number of vaccine adjuvants have been used for decades enhancing the immune response to co-administered antigens. Alum adjuvancy was

demonstrated in the early 1920s, and since then it has been incorporated in several human vaccines in the form of particulate aluminium salts, and it is still the only adjuvant approved in the USA.[20] Moreover, the triggering effect of tetanus vaccination in one case[10] provides further support to the independence of the post-vaccination phenomenon from viral strain.

Recently, a new syndrome termed 'ASIA' (autoimmune/inflammatory syndrome induced by adjuvants) has been proposed.[5] This includes post-vaccination phenomena such as arthritis, neuronal damage, fatigue, encephalitis and vasculitis. The suggested major criteria for the diagnosis of 'ASIA' syndrome include previous exposure to an external stimulus such as an adjuvant and the development of clinical manifestations such as myalgia/myositis, arthralgia/arthritis, chronic fatigue, neurological manifestations, cognitive impairment, pyrexia or dry mouth; the minor criteria include the detection of specific HLA such as HLA-DRB1 and HLA DQB1, the appearance of auto-antibodies or a defined autoimmune disease. On the basis of these suggested criteria, GCA/PMR occurring following administration of Inf-V could even be considered as a possible expression of the 'ASIA' syndrome. According to Shoenfeld and Agmon-Levin,[5] immune adjuvants may play a key role in induction of post-vaccination adverse events such as, in our case series, a specific vasculitis or a vasculitis-related disease. As Balofsky et al. suggested, increasing evidence of plausible accelerated autoimmunity/inflammation following vaccination in susceptible individuals may contribute to the development of newer and safer adjuvants, such as new oil-based examples or those that utilize Toll-like receptor signalling pathways.[21] Therefore, the identification of individual susceptibility to post-vaccination adverse events, by studying the HLA system as well as Toll-like receptor signalling pathways, could be useful in clarifying the correlation between molecular mechanisms and clinical patterns of post-vaccination phenomena.[22] The role of individual susceptibility can also explain the rarity of these events, despite the wide range of environmental factors (i.e. infectious triggers, 'natural adjuvants', etc.).

For this reason, we recommend a systematic research of previous vaccination in patients with recent onset of GCA/PMR. Although the incidence rate of post-vaccination phenomena following Inf-V is still unknown, the possibility that it could occur in the elderly population should be considered by physicians. In Italy, during the 2009–2010 influenza vaccination campaign 13,562 subjects over 65 years old, with at least one risk factor, received Inf-V, corresponding to 1.91% of all vaccinated individuals over that period.[18] We suggest strict observation for 2–6 months following administration of Inf-V of subjects at higher risk of developing GCA/PMR, such as females at a susceptible age. This may allow the identification of genetic markers of high-risk individuals in order to avoid potential immunization or reactivation of a latent disease.

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