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CASE REPORT

The Delayed-Steroid-Strategy (DSS) for Idiopathic Granulomatous Mastitis during the COVID-19 Pandemic: A Case Series

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ABSTRAK

Mastitis granulomatus idiopatik (MGI) adalah penyakit radang. Rawatannnya yang kerap menggunakan steroid mengakibatkan penerima mengalami pengurangan daya tahan imun dan meningkatkan risiko mendapat jangkitan kuman. Steroid juga boleh menghalang tindakan imun yang mencukupi selepas vaksinasi dan menyebabkan vaksin menjadi kurang berkesan. Kajian ini adalah penyelidikan yang menilai peranan dan kesan memberi 'non steroidal anti-inflammatory drugs' (NSAIDs) untuk menunda rawatan kortikosteroid. Langkah ini adalah untuk membolehkan pesakit-pesakit melengkapkan vaksinasi dan memperolehi rangsangan imun pasca vaksinasi yang memadai untuk mendapat perlindungan yang baik dari COVID-19 sebelum memulakan rawatan steroid. Ketiga-tiga pesakit ini yang baru didapati mengalami MGI telah diberi rawatan pendahuluan yang terdiri dari NSAIDs. Kesemua pesakit tidak mengadu keadaan penyakit mereka semakin teruk dalam tempoh itu.

Kata kunci: COVID-19; kortikosteroid; mastitis granulomatus idiopatik; menunda; NSAIDs

ABSTRACT

Idiopathic granulomatous mastitis (IGM) is an inflammatory disease. It is often treated with steroids which could result in the recipient having an impaired immune

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defence and increases risk of getting infections. This could also hinder an adequate immune response post vaccination and render vaccines to be less effective. This was a study to assess the role and outcome of non steroidal anti-inflammatory drugs (NSAIDs) to delay corticosteroid treatment. This strategy aims to allow the patients to achieve complete vaccination with adequate post vaccination response for better COVID-19 protection prior to commencement of steroids. All three newly diagnosed patients with IGM completed their NSAIDs bridging therapy. None of them reported any worsening of disease during that time.

Keywords: Corticosteroid; COVID-19; delay; idiopathic granulomatous mastitis; NSAIDs

INTRODUCTION

Idiopathic granulomatous mastitis (IGM) is an inflammatory disease forming granulomatous changes around ducts and lobules of the breast. It was first described by Kessler and Wolloch in 1972. The clinical findings in IGM may resemble a breast cancer (Akcan et al. 2006) and pose a dilemma in identifying the disease. The absence of diagnostic radiological features complicates the diagnosis and histopathological examination is needed to confirm the diagnosis. Despite acquiring a diagnosis, there is no standard treatment. Recurrence occurs commonly (Dağ & Edizsoy 2021). Unfavourable cosmesis may result from surgical incisions or excisions (Asoglu et al. 2005) but there are those who advocate it (Azlina et al. 2003). Currently, medical treatment consists of corticosteroids, occasionally non steroidal anti-inflammatory drugs (NSAIDs) (Mizrakli et al. 2015) while surgical excisions are performed when medications fail. The occurrence of the COVID-19 worldwide pandemic added another challenge in IGM treatment. Malaysia reported a record high of 22,242 daily cases in August 2021, with a total of 1.47 million cases and 13,302 deaths during the pandemic (Salim 2021). The government initiated a mass COVID-19 vaccination (COVAX) programme to achieve a herd immunity. During that time, the Malaysian vaccination rate appeared to be significantly higher than other neighbouring Asian and European countries (Lum 2021). Steroid treatment may result in an impaired immune defence and those immunocompromised patients were at a higher risk of getting more severe infections (Fung & Babik 2021). Therefore, the aim of this study was to discuss the role and outcome of prescribing NSAIDs as a strategy to delay corticosteroid treatment. This was to allow the patients to achieve adequate post vaccination immune response for better COVID-19 protection. With the severity of COVID-19 under control, the Malaysian government declared that Malaysia move from a pandemic to the endemic COVID-19 phase from

the 1st April 2022 (Ministry of Health Malaysia 2022). The use of NSAIDs for mastitis has been the norm in practice (cleveland clinic, nhs, mayo clinic) but clinical studies regarding its use for mastitis has not been found. However, promising data has been obtained in veterinary studies involving bovine mastitis (Breen 2017; Dan et al. 2018; Sintes et al. 2020).

CASE REPORTS

Three women, aged 26, 37 and 45 years old, were diagnosed to have IGM from July to August 2021. They were non-smokers and non-lactating with a parity ranging from two to five children. Their previous lactational period ranged from two to three years. Two of them had been on contraceptive pills for the duration of one to five years. All initial presentations were painful breast lumps for one to three months. The initial breast ultrasonography in two patients showed hypoechoic collections, suggestive of abscess formation with multiple reactive lymphadenopathies. They underwent ultrasound-guided aspiration; the purulent aspirates were sent for culture. They were then given antibiotics for the one-week duration while awaiting the culture results. Repeated ultrasound showed minimal collection. The initial pus aspirates sent for culture had no growth. The breast ultrasonography of the remaining patient showed a macro-lobulated heterogenous hypoechoic lesion, given BIRADS 4a. All women underwent ultrasound-guided core needle biopsies of the breast lesions. The pathology reports were non-caseating granuloma formation with a mixture of inflammatory cell infiltration consisting of lymphocytes, neutrophils, plasma cells and histiocytes. There was no evidence of atypical cells to suggest malignancy or corynebacterium and absence of acid-fast bacilli to suggest an infection.

All patients had not been vaccinated against COVID-19 and were not infected with COVID-19 before. They were started on NSAIDs. Two of them were given oral ibuprofen 400 mg twice a day while the other had oral diclofenac 50 mg three times a day for a duration of two months. This duration was taken in view of the COVAX programme in Malaysia, as the majority required two doses of vaccines taken at a three-week interval. The time needed to obtain adequate protection from COVID-19 was at least two weeks after the second vaccination (Malaysian Society of Hematology Consensus Statement 2021). Due to this, steroid initiation should only take place then.

All patients completed their NSAIDs bridging therapy and none of them reported any worsening or progression of disease during that time. The usual corticosteroid prescribed for IGM in our centre consists of oral prednisolone 60 mg daily for the duration of one week with a tapering dose of 10 mg every week for a total of six weeks. Persistent relapse will require a change to a second-line treatment, which is oral methotrexate. This will be given weekly starting at 15 mg with a tapering dose of 2.5 mg for a total of six weeks. Oral folic acid, 5 mg daily, will

be given on days when methotrexate is not consumed. Only with failed medical therapy, surgical excision will be offered to patients.

DISCUSSION

IGM is a benign breast disease which mostly affects women during their reproductive age (Mizrakli et al. 2015). The aetiology remains unknown. However, some studies have suggested it to be a reaction triggered by the localised immune response due to infection, trauma, contraception drugs or extravasation of secretion from breast lobules (Al-Khaffaf et al. 2008). It has been reported that 78% of women with IGM presented with a unilateral painful breast lump of various sizes (Zaragoza et al. 2013). Other common presentations include abscess or fistula formation with skin thickening, nipple retraction and axillary lymphadenopathy (Al-Jarrah et al. 2013).

The treatment of IGM has no standardised protocol. The rarity of the disease has made it difficult to create large cohorts of patients or perform randomised trials. Lai et al. (2005) proposed no treatment as complete resolution occurs in 50% of patients in 14.5 months. The general recommendations consist of medical therapy such as corticosteroids (1st line medical therapy) and methotrexate (2nd line medical therapy) followed by surgical excision if failed medical therapy. However, the medication duration and dosage vary among institutions. Some studies suggested the duration from one to twelve months of corticosteroid treatment (Akahane et al. 2013). In 1980, DeHertogh et al. suggested 30 mg per day of corticosteroids for at least two months. However, Freeman et al. (2017) had shown the possibility of achieving remission using a 16mg twice-a-day dosage. A meta-analysis showed that using corticosteroids alone resulted in a 20% risk of recurrence which was the highest compared to surgery alone or combination therapy of corticosteroids and surgery (Lei et al. 2017). The step-up approach of using methotrexate appears to be more effective in the treatment of IGM. However, its teratogenicity risk makes it a less favourable choice of medication since IGM patients are females and are in their reproductive age. Patel et al. (2010) reported that surgical excision may offer the best treatment outcome in terms of resolution of the disease but the recurrence rates are unpredictable, ranging from 5% up to 50%.

Corticosteroids usage with greater than physiologic doses may make the recipients immunocompromised and thus increase their vulnerability to be infected with pathogens; including COVID-19. Once infected, the disease may progress to become more severe (categories 3-5). The corticosteroids, at a dose of more than 20 mg per day, potentially negates the immune response from the COVAX (Kiko et al. 2016). Physicians should wait at least 2 months after discontinuation of a high dose and systemic steroid therapy which has a treatment duration greater than or equal to two weeks, before administering a vaccine to patients (Yaghan et al. 2020).

The strategy in these cases was to delay corticosteroid initiation in unvaccinated individuals upon the diagnosis of IGM, as they will usually be given high-dose steroids. The intention was to find an appropriate bridging therapy to allow those high-risk groups to obtain and complete their vaccination as soon as possible and achieve the desired immune response. The bridging therapy was NSAIDs administration with an aspiration of the abscess, if present, to be sent for culture. After aspiration of the abscess, applying ice for several minutes to numb the affected area, also bring symptomatic relief to the patients. This aims to enable the patients to complete their COVAX (usually 2 doses; 3-7 weeks apart) successfully, with the anticipated immune response allowed to occur uninterrupted for at least 1 month after the second vaccine (Pfizer, Astra Zeneca, Sinovac) or only with one vaccine as required (Cansino, Moderna) (Uysal et al. 2021). NSAIDs such as Ibuprofen or Diclofenac was given to the patients for a period of two to three months. Subsequently, the disease response was observed. All three patients on NSAIDs did not have any worsening of the disease.

Our recommendation is that, once patients have completed their vaccination, corticosteroid therapy could be initiated, if still required (Table 1). The usage of NSAIDs in IGM is mainly for symptomatic pain relief (Delgado et al. 2020). An Iranian study showed that NSAID treatment had a 65.6% positive response, a complete response of 46.1% but treatment resistance was 3.1% (Kaviani et al. 2019).

Steroid treatment has been documented to effectively reduce disease progression and thus avoid surgery. However, the ingestion of corticosteroids over a long period of time especially at high doses will put patient at risk of developing side effects such as hypertension, diabetes and osteoporosis. NSAIDs will be an ideal replacement with the ability to inhibit the inflammatory conversion enzyme such as cyclo-oxygenase (COX) as well as minimise the degree of an inflammatory process. Nevertheless, NSAIDs may potentially cause gastrointestinal side effects such

TABLE 1: The proposed timing of vaccination and steroid therapy

CASES	PROPOSED TREATMENT		
Newly diagnosed IGM or Flare up of IGM	COVAX Dose 1 NSAIDS	COVAX Dose 2 NSAIDS[c]	After 1 month, start steroid, if required to treat IGM
Any condition requiring high dose steroids (Prednisolone >20 mg/day for ≥2 weeks)	Stop steroids		After 2 months, then vaccinate (COVAX or any other vaccine used out of the Covid-19 pandemic eg. Influenza vaccine, Meningococcal vaccine etc)

IGM=Idiopathic Granulomatous Mastitis; COVAX=COVID-19 vaccination; NSAIDS=Non steroidal anti inflammatory drugs

as gastritis and ulceration; which did not occur in our cohort of patients. To avoid this, it has been our practice, to prescribe a proton pump inhibitor such as pantoprazole 20-40 mg daily, at the initial half (3 weeks of a 6-week course). As NSAIDs are nephrotoxic, it must be used cautiously in those with renal impairment.

NSAIDs generally inhibit COX. COX are divided into 2 iso-enzymes, which are COX-1 and COX-2. Inhibition of COX-1 will prevent production of prostaglandins and thromboxane. Prostaglandins from COX-1 are important for gastrointestinal and renal function whereas thromboxane is important for platelet function. Inhibition of COX-1 for long periods will increase the risk of gastric and renal problems and may impair blood clotting. Another option is to use selective COX-2 inhibitors that only act on the prostaglandins which cause inflammation, pain and fever (Breen 2017). The COX-2 inhibitors that are currently available include Celecoxib, Etoricoxib, Parecoxib (Zarghi & Arfaei 2011) and Meloxicam (Schattenkirchner 1997). Although selective COX-2 inhibitors have no or minimal effect on the gastrointestinal, renal and platelet function, they are more expensive and increase cardiovascular risks which have led to some of them, such as Rofecoxib and Valdecoxib, are withdrawn from the market.

CONCLUSION

This study has shown that NSAIDs can be used as a bridging treatment for IGM during the COVID-19 pandemic in order to enable patients to obtain COVAX to optimise their safety. Bridging treatment using NSAIDs may also be applicable in other diseases that require high-dose steroids until the patients have their vaccinations.

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