Review Article

Idiopathic Granulomatous Mastitis: A Management Dilemma

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Abstract

Idiopathic Granulomatous Mastitis (IGM), or Granulomatous Lobular Mastitis (GLM) or simply GM (Granulomatous Mastitis) is a benign chronic and sometimes recurrent inflammatory process of unknown etiology, involving one or both breasts, commonly in women of childbearing age. In has no definite diagnostic hallmark or marker. It is to be diagnosed by exclusion of all other diseases. Biopsy is mandatory. A challenge is there to differentiate IGM from other diseases including malignancy, tuberculosis and other granulomatous reactions, It has no specific curative treatment. Breastfeeding from the IGM breast is safe, if not on immunosuppressive or steroid treatment. It has long been classically treated with oral steroids with or without such other immunomodulators as methotrexate, azathioprine etc. Recently, intralesional triamcinolone injection has been shown to improve the symptoms. But local high concentration intralesional triamcinolone, systemic immunosuppressive agents are unsafe for breastfed babies. If a woman chooses systemic treatment, after Shared Decision Making (SDM), she should be cautioned about milk suppression and untoward effects both in mother and baby. Some women prefer no medication during lactation. Complicated cases or failure of conservative treatment calls for surgical treatment in the form of local wide resection or mastectomy etc. The patients may suffer physically, mentally, and economically, significantly lowering the quality of life. There is no consensus on its management strategies. Its management still remains as a challenge. We like to review, discuss, and share about its masked etiology, presentations, diagnostic aids plus the available avant-garde optimum management strategies.

Key words: *Autoimmune mastitis, Granulomatous inflammation, Non-caseating and Non-necrotizing granuloma.*

Date received: *16.09.2022*

Date accepted: *20.11.2022*

DOI: https://doi.org/10.3329/kyamcj.v13i4.65035

KYAMC Journal. 2023; 13(04): *250-256.*

Introduction

IGM is a rare benign, non-life-threatening chronic and sometimes a recurrent heterogeneous nonspecific inflammatory condition of one or both breasts of unknown etiology, usually without gross necrosis, (as opposed to gross caseous necrosis of tubercular granulomatous mastitis, etc.), usually in women of child-bearing age (mostly between 20 to 40 years of age).[1-3] Granulomatous changes occur around lobules and ducts of the breast (lobulo-centric granulomatous inflammation) in the absence of any known specific infection, trauma, sarcoidosis, Foreign Body (FB), known autoimmune disease etc. IGM has been linked to pregnancy, breast-feeding and oral or injectable contraceptives. A probable autoimmune etiology is suggested. That is the cause may be an autoimmune reaction to an unknown infection or any other factor. It may be chemical reaction that is likely to be associated with oral contraceptive pills, or even lactation. Other associated common finding of granulomatous lesions of the breast and axilla include silicone granulomas, fat necrosis and suture granulomas. In many cases, no associated agent is found and the clinical history is consistent with idiopathic granulomatous mastitis.[4-6]

Historical aspects

IGM was first explained histopathologically by Kessler and Wolloch in 1972 as a benign disease entity. Since then, several hundreds of case reports have been documented from all over the world.[7,8]

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Incidence and prevalence

Its exact incidence is unknown. Though almost always it is described as an uncommon condition, IGM is not so much uncommon. For the last two decades, it is being increasingly reported. Since its first description in 1972, over hundreds of cases have been reported from all over the world. Nevertheless, IGM is a rare differential diagnosis with an estimated incidence of about 2.4 per 1 lac women and 0.37% in the United States. It is detected more in in non-white women, and the incidence in Europe is probably less, particularly in Germany.[9-11]

Etiology

Its exact etiology is totally obscure and hypothetical. Because of rarity and less research-work on IGM, there are no valid data as regards to its etiology. As per current data, etiologically, it is not a microbial or protozoal or any other parasitic disease. Possible autoimmune theory or hypersensitivity reactions are suggested by some researchers, i.e., an autoimmune disease limited to the breast. Staphylococcus aureus, Propionibacterium acne and Corynebacterium species had been isolated from few cases. Another hypothesis claims that the granulomatous mastitis is a reaction to luminal secretions leaked into the peri-lobular connective tissue following to epithelial injury by some unidentified mechanism. In many cases, IGM is found to be associated with idiopathic hyperprolactinemia.[12-14]

Pathology

A granuloma is a focal zone of chronic inflammation. A granulomatous inflammation is a specialized type of chronic inflammation characterized very often by localized collections of macrophages (activated histiocytes), epithelioid cells (early macrophages) and multinucleated giant cells. Granulomas develop when antigens are resistant to such "first-responder" inflammatory cells as neutrophils and eosinophils. Chronic granulomatous disease (CGD) is said to occur in an immunodeficient condition caused by defects in phagocyte enzyme, NADPH oxidase, resulting in failure of killing such infective agents as bacteria and fungi after phagocytosis, and thus increasing infections, more often characterized by extensive granuloma formation.[15-17] Mutations in one of five different genes can cause these defects. Granulomatous inflammations are found in various pathological processes including infection, autoimmunity, toxicities, allergy, drug reactions and neoplastic conditions. The tissue reaction pattern varies a bit specifically with significantly narrowing the gaps in the pathologic and clinical differential diagnosis and consequent clinical management strategies. All mycobacteria are more or less associated with granuloma formation. Granulomas were traditionally being incriminated as a pathological hallmark of tuberculosis. In granulomas, there are protective arrays of immune cells with an attempt to contain the invading pathogen. However, granulomas can also undergo changes, developing caseums (central caseous materials where bacteria can thrive) and cavities that facilitate bacterial spread and disease progression. Typical mycobacterial infections are characterized by caseous granulomas where macrophages, such highly differentiated cells as multinucleated giant cells, epithelioid cells and foamy cells are surrounding the central cheese-like necrotic region (central caseous necrosis) with a rim of lymphocytes of both T- and B-cell types around the phagocytic cells. Caseating and caseous granulomas mean necrosis involving dead and destroyed cells, which are being converted into centrally located amorphous greyish debris (caseous material), having no nuclei and no nucleated cell in caseated material. Mycolic acid and other lipid constituent of the mycobacteria cell wall confers a characteristic "cheese-like" appearance in the granuloma of tuberculosis. Hence the descriptive term, "caseous" is there. Caseous necrosis is the most commonly found in tuberculosis. Caseating granulomas may also formed by various fungal infections, Treponema pallidum (tertiary stage). Noncaseating granulomas and granulomatous inflammation may be formed by other inflammatory condition (e.g., sarcoidosis and Crohn disease), vasculitis, Wegener granulomatosis, rheumatoid arthritis, berilyosis, drug reactions, FB (Foreign Body) reactions, Tularemia, Cat-Scratch Disease (CSD), idiopathic granulomatous mastitis (IGM), NTM (Non-tuberculous Mycobacteria), and some other fungi. Atypical mycobacteria (photo-chromogens, scoto-chromogens, non-chromogens, and rapid growers) produce fewer granulomatous changes and a greater degree of acute inflammation with abscess formation than those caused by typical mycobacteria (M tuberculosis hominis, M tuberculosis bovis).[18-20]

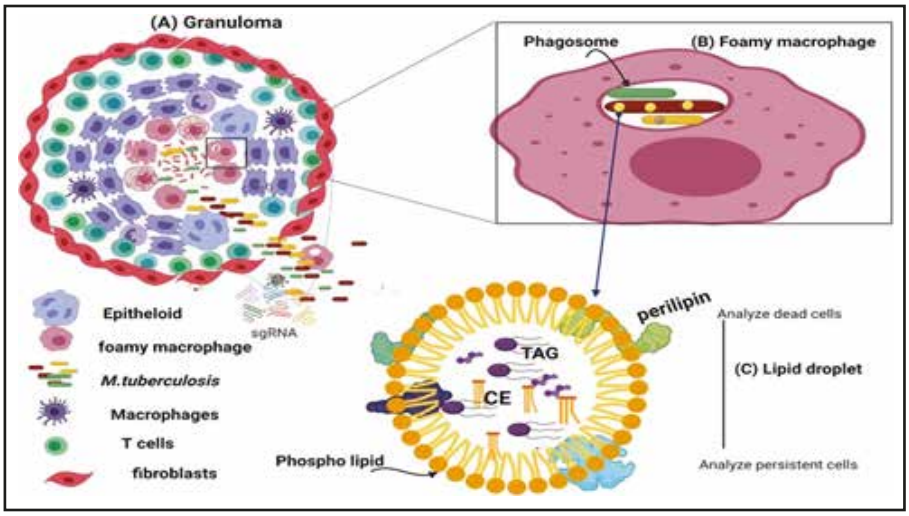

Fig.1: Caseating Granuloma of typical tuberculosis. (Courtesy: ResearchGate).

In addition to massive caseation or caseating found in tertiary syphilis, rarely a prominent histiocytic inflammatory infiltrate may be seen in lesions of secondary syphilis as well. Though granulomas are classically described as a benign condition, malignant lymphoma is one of the potential underlying causes of granuloma. Notably, some prominent granulomatous lesions may mask the morphologic changes in lymphomas. Cutaneous granulomas of rheumatoid arthritis (RA) are characterized by aggregation of activated histiocytes (macrophages). Sarcoidosis is a multi-system and multi-organ disease of unknown etiology, characterized by noncaseating epithelioid granulomatous inflammation, and it is sometimes misdiagnosed as tuberculosis, though some researchers claim that sarcoidosis is an autoimmune related disease. Sarcoidosis starts as tiny, grain-like lumps, called granulomas in different organs including skin, lymph nodes, lungs and many other soft tissues. Sarcoidosis has a higher prevalence in European countries. Leprosy is also a chronic granulomatous disease caused my M lepare. Granulomatous uveitis and non-granulomatous uveitis are well-known entities. Non-caseating granulomas are also present in 60% of Crohn enteritis. Granulomas of any form were never recognized in ulcerative colitis. Very rarely, a granulomatous reaction to concurrent carcinoma breast is present and a biopsy is essential to diagnose malignancy.[11,21,22]

The histopathological examination of biopsy specimens in granulomas has been thought to reflect to some degree the integrity of the IFN-γ/IL-12 pathways. Normally, control of mycobacterial infection is associated with granulomatous reaction having central macrophages and surrounding lymphocytes. But the loss of either IFN-γ through genetic means or TNF-α through pharmacologic cause, granulomas disappear. Therefore, patients with recessive complete IFNγR1 or IFNγR2 deficiency have virtually no or very poorly organized granuloma formation, but have macrophages diffusely loaded with AFB (Acid-Fast Bacilli). Ill-defined granulomas were seen in some patients with AR IRF8 deficiency or IL-12Rβ1 deficiency. Patients who have preserved granuloma formation are probably based on their ability to produce IFN-γ through pathways other than IL-12. However, in several recent cases of NTM infections, IL-12Rβ1 deficiency without any granulomatous response have led to re-evaluation of the retained granuloma formation in IL-12Rβ1 deficiency states. It appears to have a correlation between the type of granuloma formation and clinical outcome, as more poorly-differentiated granulomas being associated with poorer prognosis.[23-27]

Clinical Features

Clinically, IGM has a spectrum of manifestations ranging from localized breast lumps through abscesses, fistulation, sinus formation, features of acute inflammation to extensively large lesions often mimicking a mastitis carcinomatosa. Most commonly, it occurs in women of child bearing age, mostly 20 and 40 years of age, frequently found with recent conception or pregnancy or lactation or hormonal contraceptive use, often presenting as a palpable tender ill-defined lump of variable sizes. Exceptionally, it had been described in a girl 11-year-old, in a woman of 80-year-old, and in a male with gynecomastia. It may be bilateral, but most often it is unilateral. Clinically it may be misdiagnosed as carcinoma breast or tubercular or lactation al or periductal mastitis. It can develop in any part of the breast, but most commonly it starts or retro-areolar in position, with or without extension peripherally or axillary lymphadenopathy. It may be persistent or recurrent. Patients with idiopathic granulomatous mastitis usually don't have extra-mammary granulomatous disease. The most common clinical presentation is a firm, unilateral, and discrete breast mass that is often associated with an micro-abscess formation or inflammation of the overlying skin, induration, ulceration or fistulation or sinus formation, nipple retraction, areola retraction, skin tethering etc.[16,28,29]
IGM in early stage commonly presents as a painless, ill-outlined, firm to hard, rarely soft, non-tender, unilateral lumpy mass which is impossible to differentiate from a breast malignancy. It is most commonly not associated with palpable axillary lymph nodes. IGM at late stages usually present with a florid inflammatory condition, including an ill-defined acutely inflammatory mass (features of acute inflammation become overt), pain, and redness (erythema), hyperemia, areolar retraction, nipple retraction, skin retraction, edema, and peau d'orange etc. simulating mastitis carcinomatosa, with or without one or more fistulae or sinuses or ulceration, micro-abscesses, cyst-like lesion, nipple discharge etc.[20,30]

Complications

Complications include infection, psychological upset, sinus tract formation, fistula formation, Recurrence, persistence for over several years, conjugal disharmony etc. invariably increasing anxiety, psychogenic depression, lowering quality of life.[21,31,32]

Diagnosis

There is no definite diagnostic hallmark for IGM. It is a presumptive empirical diagnosis that is being suggested after exclusion of all other probable diseases. A complete history taking, thorough physical examination, routine, specific and special laboratory investigations, particularly imaging and histopathological examinations are to be undertaken.[33]

Blood prolactin levels are often higher in some women with IGM. The caring consultant is to exclude both malignancy and other types of mastitis, e.g., tubercular mastitis, autoimmune mastitis, sarcoidosis, interstitial mastitis, periductal mastitis (mammary duct ectasia/plasma cell mastitis), lactational mastitis, syphilitic mastitis etc. Markers of autoimmune diseases (e.g., titers of rheumatoid factors (RF), serum complement, anti-neutrophil cytoplasmic autoantibody (ANCA), c-ANCA, interleukin 2 receptor, or angiotensin-converting enzyme and anti-dsDNA antibodies) are usually within normal limit in IGM. There may be nonspecific increase in CRP (C-reactive protein). Usually there is normal values of carcinoembryonic antigen and cancer antigen (CA) 15.3 etc.[15,18]

Fine Needle Aspiration Cytology (FNAC) in cases of IGM reveals commonly epithelioid macrophages, giant cells and neutrophils, absent necrosis & no other specific features. So, the diagnosis is inconclusive. Mammography shows IGM as nonspecific nodular heterogeneous opacities or an ill-outlined mass of variable density. Mammography occasionally may mimic breast cancer. Sonography shows nonspecific hypoecho

ic complex lesions or localized micro-abscess-like or cyst-like lesions. Rarely, multiple clustered, often contiguous hypoechoic masses are seen on imaging. MRI (Magnetic Resonance Imaging) findings are similarly equivocal and nonspecific. MRI may be more useful to exclude a malignant disease, that is expected to reveal normal and destroyed mammary parenchyma, but still it is non-conclusive. These imaging findings, like all other clinical features cannot exclude malignancy or other types of mastitis. Thence biopsy (Cor-cut-needle biopsy, incision, or excision biopsy) is mandatory to exclude diseases other than IGM. Histopathological features of IGM are predominant lobular inflammatory process and that of non-caseating granulomas (having epithelioid macrophages and Langhan's multinucleated giant cells, variable numbers of Lymphocytes, plasma cells and eosinophils, often polymorphs, with or without foamy macrophages, micro-abscesses, fat necrosis, occasional non-caseating nonspecific necrosis, duct dilatation, epithelial ulceration, luminal neutrophils) centering on lobules, where the inflammatory reactions sometimes extend into interlobular areas. Caseating necrosis is not present. Inflammation can extend into and involve adjacent lobules, sometimes the whole breast may be involved. Parenchymal acinar structures and ducts may be damaged and lost. No vasculitis, FB (foreign body) are found. Gram's staining, Special staining (Ziehl-Neelsen, periodic acid Schiff etc.) are all negative for any specific organism. Culture in different ordinary and special media, immunohistochemistry, DNA probe tests, PCR studies fail to reveal any specific causative microbe or other parasite. Thus, biopsy or repeated FNAC exhibits a nonspecific inflammatory condition with no evidence of malignancy or tuberculosis, which helps differentiating the lesion from a cancer or tuberculosis. Gross naked eye features include Ill-defined soft tissue mass of variable sizes are usually found. The gross macroscopic features are not distinctly diagnostic. The definitive way of presumptive diagnosis relies on the availability and sophistication of diagnostic aids and trained staff to interpret the results. Thus, IDG is to be diagnosed by exclusion of other diseases.[4,13,28,29]

Differential Diagnosis

As there is no definite diagnostic hallmark for IGM, almost all breast diseases should be considered in differential diagnosis. Important ones include carcinoma breast (specially inflammatory breast cancer/mastitis carcinomatosa), tubercular mastitis, MDAIDS (Mammary Duct-Associated Inflammatory Disease Sequence) including periductal plasma cell mastitis (mammary duct ectasia), Interstitial mastitis, lactational mastitis, mammary sarcoidosis, breast abscesses and chronic suppurative mastitis, nocardiosis, Wegener's granuloma, giant cell arteritis, erythema nodosum, polyarteritis nodosa, vasculitis, rheumatoid arthritis, berilyosis, drug reactions, foreign body reactions, Tularemia, Cat-Scratch Disease (CSD), lymphocytic lobulitis, actinomycosis, IgG4-RD mastitis, autoimmune mastitis, all types of infective mastitis and such fungal disease as histoplasmosis etc.[3,5,17]

Treatment

Like diagnosis, treatment of IGM patients is very often challenging. Various treatment approaches include observation, wide local excision, systemic steroids, immunosuppressive agents, and occasionally mastectomy. Once cancer and other differential diagnosis have been excluded, the best treatment is yet unknown. If there is hyper-prolactinemia, anti-prolactin drug therapy is advocated. For patients with mild symptoms, a trial of observation, local excision, or steroids may be indicated. Intensive follow-up is required. Surgical excision is not mandatory if the lump is asymptomatic. Here, careful observation and follow-up are entrusted with belief that the disease is not commonly so much serious, sometimes self-limiting (may be cured spontaneously by 1 to 2 years follow-up without any medication), and unlikely to get worse. A wide local excision with free margin is claimed by someone as the definitive treatment in early stages of IGM.[15, 29,32] If there are progressive symptoms or if presenting with severe or generalized involvement of breast, a trial of steroids (oral prednisolone) is indicated that can relieve symptoms. Remission may be obtained with a 1- to 2-years course of low-dose methotrexate or azathioprine and prednisolone. Mastectomy is warranted only if there are intractable symptoms (like intractable pain). Recurrence after surgical excision is not rare and complications like abscess formation, fistulation, sinus formation, suspicious lump are indications for surgery. Repeated excision is discouraged and not approved. If the lump is painful or getting worse or getting bigger, or if an exact diagnosis could not be established on core-cut-needle biopsy alone, complete excision should be undertaken for definite diagnosis, exclusion of malignancy and to undertake appropriate staining or other tests to exclude other pathology. Then, IGM may typically be treated by steroid as the disease is assumed to have an autoimmune basis. Oral Prednisolone 60 mg/day may be given for 6 weeks. If there is extensive IGM, it doesn't warrant excision, preoperative treatment with steroids, nonsteroidal anti-inflammatory drugs, or colchicine may allow for more conservative surgical procedures later on. Abscesses may need to be drained. Fistula or sinus tracts may need to be excised. Antimicrobials are advised if there is secondary infection, that are best chosen in accordance to the culture and sensitivity reports. Trimethoprim and sulfamethoxazole combination against bacterial infections, and itraconazole for fungal infection may be sometimes worthwhile. Immunomodulators (like steroids, methotrexate, colchicine, azathioprine etc.) are very often helpful in selected progressive or extensive or recurrent cases. Sometimes, it needs continued Immunosuppressive therapy until complete remission. Medical board (comprising immunologists, infectious disease physicians, hematologists, and oncologists, surgeons) needs to be occasionally formed for total and successful management.[1,2,24] Conservative approach in relapse cases needs immunosuppression (steroids and methotrexate, azathioprine, colchicine etc.), and the clinical course may last for about 1 to 2 years or more before resolution. Surgery may then be avoided. A stem cell transplant may cure CGD. Decision for stem cell transplantation relies on multiple factors that include prognosis, donor availability, individual's choice and consent. The value of immunotherapy has not yet been confirmed.[1,2,12, 29]

Discussion

IGM is said to be uncommon, though it is not that much uncommon. It is an episodic disease, and it can develop in any premenopausal women and can present either as a palpable

tender mass or as a collection of micro-abscesses. However, it has been documented in girls, elderly women, and males. That is to say that probably no age and no sex are immune to IGM. Essentially, IGM is a heterogeneous disease with varied clinical features at presentation, that puts the clinicians into a diagnostic and therapeutic dilemma. Thence, with a high degree of clinical suspicion, it is to be managed. Updated reviews still confirm its obscure etiopathogenesis. It may be bilateral in about 25% patients. In up to 50% patients, clinically it may be misdiagnosed as carcinoma breast or other inflammatory breast disease.[5,12] Some researchers claimed that the inflammation of IGM is a reactionary response to trauma or metabolic or hormonal factors or autoimmunity or an implication with such microbes as Corynebacterium kroppenstedtii. Although the current knowledge suggests the IGM is a non-infectious disease, although many authors including Taylor et al suggested that the species of corynebacterium is a major etiological aspect Following this, several other case reports were documented where presence of different species of corynebacterium (C. tuberculostearicum, C. freneyi, and C. kroppenstedii), corroborated the theory of Taylor et al. In case series from a Japan, C. kroppenstedii was isolated from several cases. It may be that C. kroppenstedii within IGM lesions speaks about a subgroup of the disease named 'cystic neutrophilic granulomatous mastitis'; because cystic spaces or vacuoles were found among granulomatous and neutrophilic inflammation. Several other researchers explain that corynebacteria are there as a contaminant from the normal skin flora.[17-19]

The management of GM is controversial. Triple assessment clinical, imaging, and pathological) is needed to arrive at a presumptive diagnosis. Excluding other diseases, IGM (Idiopathic granulomatous mastitis) is diagnosed. Infective etiology is excluded by special tests for tuberculosis and fungi. Special staining and culture of tissue for tuberculosis and fungi should be performed. Sarcoidosis is histopathologically similar and its clinical lesion in other organs and sites should be sought. In Wegener's granulomatosis a vasculitis may be detected and respiratory tract and renal disease should be sought. Granulomatous inflammation may also be found in association with mammary duct ectasia; however, the inflammation is localized on ducts and not in lobules and there is evidence of duct dilatation. Such other chronic inflammatory processes as mammary duct ectasia, sarcoidosis, tuberculosis, and (seen in young insulin-dependent diabetic women) need to be excluded. Failure of initial management strategies should prompt tissue biopsy (and diagnostic imaging) to exclude malignancy. Tissue from core-cut-needle biopsy or incisional biopsy or excisional biopsy is to be sent for AFB (Acid-Fast Bacillus) and fungal stains to diagnose or exclude tuberculosis or nocardia or other fungus. FNAC (Fine-needle aspiration cytology) is here worthless.[13,14] Ultrasound, mammography, and magnetic resonance imaging (MRI) are considered as non-specific. Typical findings on ultrasound are multiple contiguous hypoechoic masses with posterior acoustic shadowing or posterior acoustic enhancement. Advanced cases present with fluid collections and cavities in association with skin fistulas. Most cases present with hypervascularity which can be detected by Doppler imaging. 15-55% of all cases show ipsilaterally enlarged reactive axillary lymph nodes. Mammography shows unilateral focal or regional asymmetry as the most frequent pattern, but in 24% it fails to identify an abnormality. Lesions were mammographically occult in 15 out of 45 women, possibly because of an overlying dense breast pattern seen in most women (36 out of 45).[10,11] MRI findings are also variable and can show heterogeneous ill-defined masses and non-mass enhancement depending on the severity of the inflammation. Fazzio et al. describes T2 hyperintense, peripherally enhancing masses with central areas of non-enhancement representing abscess formation, as is typical for advanced cases.[3,6]

Immunologic assessment and evaluations for NTM (non-tubercular mycobacteria) infections are challenging as diagnostic tests and assays are complex. Some of these diagnostic tests and assays are available only in research centers. The importance of getting genetic molecular diagnosis is variable as being dependent on age and other such variables of the patient as transplant requirements and family implications etc.[1,5,30]

Most clinicians initially treat with antibiotics and corticosteroids, followed by continuous steroid therapy, and if required surgery is undertaken for persistence disease.[4]

In brief, treatment options fall into two groups

1. a conservative strategy involving medical therapy with corticosteroids, and 2. a surgical approach.

At the time of clinical presentation, 33% patients have abscess-like symptoms such as pain, erythema, as well as a mass, fluid collection on ultrasound, and reactive lymphadenopathy. These patients may undergo abscess puncture, drainage, or incision depending on the size of the lesion. Aspiration can fail because the abscess-like mass often has necrotic tissue in the center that makes the aspirate thick and hard to extract.

In 1980, De Herthogh et al. first suggested a high-dose corticosteroid therapy with prednisolone 30 mg/day for about or at least 2 months. This causes decrease in size the lesion despite its side effects (e.g., weight gain, hyperglycemia, Cushing's syndrome). Despite these untoward side effects, this treatment strategy then became a standard of ideal care.[3,5] Freeman et al. suggested a lower-dose regimen of 16 mg prednisolone two times daily for 2 weeks, and then slowly tapering over 2 months. This strategy then failed.[15] A group German clinicians had shown the success of a high-dose treatment of prednisolone up to 1 mg per kg per day for 2 to 6 months. Surgery could be avoided in many of these patients. Here 15% patients had shown recurrence following apparent cure.[19] By some researchers, there were ongoing trials to reduce the oral/systemic steroid dose. amd the corticosteroid exposure of the patient, using topical 0.1% hydrocortisone butyrate cream twice a day on alternate days versus wide local excision; but they had failed to draw a conclusion.[1,3] The use of methotrexate during child bearing age after failed corticosteroid therapy is still not universally accepted worldwide.[5,8] An alternative approach is surgical wide excision to mastectomy depending on the individual patient's demand, divergent regional resources, the patient's expectations, and surveillance opportunities. Most surgeons prefer a wide excision of the granulomatous lesion.[9,10] Still there

is no uniform consensus or no guideline as regards to the surgical or medical approach. A blind antibiotic therapy is usually given without any microbiological proof of a bacterial infection. IGM is per definition a sterile inflammatory disease; therefore, antibiotic therapy usually fails.[12] Antibiotics have the lowest effectiveness in the treatment of this abacterial mastitis with apparent improvement rates ranging from 6 to 21% . Corticosteroids have a success rate of between 66 to 72%. In a meta-analysis by Lei et al., a pooled recurrence rate for oral corticosteroid therapy was 20%. Surgery per se or in combination with steroids may have the lowest recurrence rates of 6.8 and 4%, respectively. Typically, the microbiological cultures are negative. Cultures positive for Corynebacterium spp. are of no consequence for the actual therapeutic strategy as so far there is no effective treatment against corynebacteria; most antimicrobials are hydrophilic with weak distribution to lipid environments.[17] The genetics related mycobacterial pathology has been clarified through the studies relating nontuberculous diseases by NTB. Some monogenic faults linked to Mendelian susceptibility to BCG and NTM have been detected, though many of these faults practically apply only to disseminated disease. Before the advent modern antimicrobial agents, IGM patients died of secondary infection and consequent sepsis. Thence initially it was designated as a "fatal granulomatous disease". Now IGM is now regarded as a benign non-fatal disease, if not complicated.[17]

Prognosis

Patients of IGM may have severe symptoms for a while, but then symptoms may clear up with or without treatment and the affected breasts usually return to normal or near normal by several years. Or, IGM may last for 12 months or more before healing occurs. Early diagnosis and treatment can significantly improve the prognosis. Persistent disease lasting for over several years may be rampant. Apparent response to steroid therapy is recognized. Some patients need surgical treatment with a risk of recurrence, clinically simulating wound infection. Recurrence rate may be as high as 50%, that can occur after several months to years emphasizing the need for long-term follow-up.[29,30]

Conclusion

As there are high incidences of malignancy and omnipresent TB (tuberculosis), malignancy and TB are considered firstly in the differential diagnosis of granulomatous diseases of breast. Detailed assessment and evaluation are to be followed for appropriate presumptive diagnosis, and differentiation from other causes of granulomatous diseases, thus to ensure appropriate treatment approaches.

Recommendations

As etiology of IGM is unknown, there is no way to prevent it. Although, it is a rare disease, it needs multi-center studies and meta-analysis for more elaborate understanding, earlier exact diagnosis, the best specific treatment and prevention of recurrence.

Acknowledgment

We are extremely grateful to our respected Prof. Md. Zulfikar Ali of the Department of Medicine and Gastroenterology of Khwaja Yunus Ali Medical College, Enayetpur, Sirajganj for his kind inspiration and encouragement in preparing this review article entitled 'Idiopathic Granulomatous Mastitis As A Management Dilemma' for publication in this esteemed KYAMC journal.

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