Heart failure associated with rheumatoid arthritis

Abstract :

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joints. Extra-articular features are very common. We report a case of RA first diagnosed after an episode of congestive heart failure (CHF) and the evolution of left ventricular function after conventional treatment of CHF and immunosuppressive drugs. The patient, a 52-year-old man, with history of epilepsy and a stroke 6 years before, presented to the emergency department with increasing dyspnea. He had polyarthralgia 2 months before. The lower extremities had mild pitting edema. The musculoskeletal examination revealed synovial thickening of the metacarpophalangeal and proximal interphalangeal joints, but there was no joint tenderness. The patient's alanine aminotransferase, troponin levels and CRP were slightly elevated. His renal function was preserved. The electrocardiogram (EKG) was normal. An echocardiogram performed in showed a global hypokinetic dilated cardiomyopathy with an ejection fraction of 15–20%, with apical thrombus. The patient was diagnosed with exacerbation of congestive heart failure (CHF) and was treated with intravenous diuretics. This led to symptomatic improvement. He got a conventional heart failure treatment with vit K antagonists. Coronarography was normal. Viral serologies were negative. The martial, phosphocalcic and thyroid markers were normal. However, the immunologic tests showed positive rheumatoid factor and anti-CCP. The diagnosis of dilated cardiomyopathy due to rheumatoid arthritis was retained. The patient was treated by corticosteroids and immunosuppressive agents. Patient was seen during routine follow-up after 6 months. Interestingly, echocardiographic findings were totally normal with left ventricular ejection fraction >50% and normal LV size.

Keywords : rheumatoid arthritis, Heart failure, cardiovascular complications of rheumatoid arthritis

Introduction :

Cardiovascular features in rheumatoid arthritis (RA) are common. Among those are the classical extra-articular features that not only include pericarditis, cardiomyopathy/myocarditis, cardiac amyloidosis, coronary vasculitis, arrythmia and valve diseases, but also congestive heart failure and ischaemic heart disease which are found more frequently and are associated with an increased mortality compared with the general population. There is a general consensus that a 1.5 multiplication factor is used when using unadapted cardiovascular disease (CVD) predictor algorithms in patients with RA [1]. This increased risk is independent of traditional risk factors such as age, smoking, gender, hypertension, and hyperlipidemia.

Several drugs are used in RA, including corticosteroids, immunosuppressive agents, biological therapy. They have an important positive effect in the reduction of arthritis activity and improvement of functional capacity, but can also be incriminated in possible deleterious effects on heart function.

We report a case of RA first diagnosed after an episode of congestive heart failure (CHF) and the evolution of left ventricular function after conventional treatment of CHF and immunosuppressive drugs.

Case report:

The patient, a 52 year old man, with history of epilepsy and non-documented stroke 6 years before, presented to the emergency department with increasing dyspnea. He had had stable dyspnea on exertion of 1 city block for 1 year but never received any medical care. Three weeks prior to admission, the patient had developed dyspnea at rest and orthopnea. In addition, he had experienced polyarthralgia for 2 months. He denied having any episode of chest pain, fever, cough, sore throat, myalgias, headaches or rhinorrhea.

The patient was in moderate distress from dyspnea. However, he was afebrile and had an oxygen saturation of 92% on room air and 97% on 4 liters by nasal cannula. He was slightly tachypneic with a respiratory rate of 20 breaths/minute, and his heart rate was 100 beats/minute and regular.The initial blood pressure was 126/62 mm Hg. The peripheral pulses in the upper and lower extremities were strong and symmetric. On cardiac examination, the patient had no murmurs, rubs, or other adventitious sounds. Lung auscultation revealed rales throughout the lung fields, most evident at the bases. There was no hepatic engorgement and no splenomegaly. The lower extremities had mild pitting edema. The musculoskeletal examination revealed synovial thickening of the metacarpophalangeal and proximal interphalangeal joints, but there was no joint tenderness.

Results of the initial laboratory workup are shown in Table1. The patient's alanine aminotransferase, troponine levels and CRP were slightly elevated. His renal function was preserved. An electrocardiogram (EKG) revealed normal sinus rythm (75 beats/minute) . There were no ST segment or T wave abnormalities, and no sign of left ventricular hypertrophy.

A chest radiograph revealed cardiomegaly and Kerley B lines (Figure 1).

An echocardiogram performed in the emergency department showed a global hypokinetic dilated cardiomyopathy with an ejection fraction of 15–20%, with apical thrombus (figure 2).

Table 1: Results of laboratory tests

Hb	**13,5 g/dl**
White cells count	17960
Neutrophils	
Lymphocytes	
Eosinophils	
Urea	0,7 g/l
Creatinine	11 mg/l
ASAT	154 UI/l
ALAT	74 UI/l
CRP	230
LDL	1,28
Troponin hs	139 -> 141 ug/l (after one hour)
Hemocultures	3 negatives

Initial management

The patient was diagnosed with exacerbation of congestive heart failure (CHF) and was treated with intravenous diuretics. This led to symptomatic improvement. He was in stable condition after 2 days in intensive care units and was put under conventional heart failure treatment: spironolactone 50mg/day Ivabradine 2,5 mg/day, Ramipril 2,5 mg/day and was anticoagulated with vit K antagonists (acenocoumarol).

Etiologic investigations:

Several investigations were performed in order to diagnose the etiology the patient's hypokinetic dilated cardiomyopathy. Regarding his gender, history of stroke and LDL levels, a coronarography was first performed and returned normal.

Biological tests were carried out in search of metabolic, immunological and viral abnormalities. Viral serologies were negative. The martial, phosphocalcic and thyroid markers were normal. However, the immunologic tests showed positive rheumatoid factor and anti-CCP. Anti-DNA, anti-ENA, anti-SSA, anti-SSB, Anti-phospholipids, anti-b2-glycoprotein, and ANCA were all negative. (table 2)

Final diagnosis:

The diagnosis of dilated cardiomyopathy due to rheumatoid arthritis was retained. The patient was transferred to internal medicine department were he was put under corticosteroids (3 intravenous bolus of 1g solumedrol, with oral relay) and immunosuppressive agents (cyclophosphamide 1g/ month during 6 months)

Follow-up:

Patient was seen during routine follow-up after 6 months. Interestingly, echocardiographic findings were totally normal with left ventricular ejection fraction >50% and normal LV size with completely resolution of thrombus (figure 3)

Discussion:

In more recent publications, pericarditis is still encountered as the most frequent finding in echocardiographic series, with incidences ranging between 30% and 50% (2). In contrast, the epidemiology of RA associated cardiomyopathy/myocarditis is less well explored. A study reported that 7 (25%) of 28 patients with RA had increased myocardial uptake in gallium scintigraphy, possibly consistent with myocardial inflammation(3). In a recent autopsy study of 81 patients with RA who died in the hospital, 13 (16%) died of heart failure, whereas in the age- and sex-matched control group of 243 non-RA patients, only 8 (3%) patients died of heart failure. Variable changes were noted in patients with RA carrying the diagnosis of heart disease prior to death, including pericarditis, myocarditis, angiitis, microinfarcts, granulomatous lesions, and amyloid deposits (4).

Patients with RA seem to have not only the CHF risk associated with IHD and traditional cardiovascular risk factors that is observed in the general population, but also an additional risk apparently not associated with traditional cardiovascular risk factors or clinically overt IHD, which contributes to their excess mortality. Several possible etiologic mechanisms involved in the increased

risk of CHF in patients with RA have been described. Results of recent studies suggest that in the elderly population, higher levels of systemic markers of inflammation predict the risk of CHF (5), even in the absence of MI (6). Other possible explanations include a higher prevalence of unrecognized or subclinical IHD and/or cardiovascular risk factors that could, at least partially, promote CHF. Pericardial and valvular disease, which are possible complications of RA (7), and the potential cardiotoxic effect of RA drugs such as nonsteroidal anti-inflammatory drugs (8), corticosteroids, chloroquine (9), D-penicillamine (10), or biologic agents (especially tumor necrosis factor inhibitors) may also play a role.

In our case report, HF conventional treatment associated with glucocorticosteroids and cyclophosphamide leaded to total regaining of LV ejection fraction (15 % -> >50%). However, data in literature is more nuanced.

The treatment of HF in patients with RA is similar to that in those without RA. In terms of RA therapy, paradoxally, medications used in the treatment of RA may also contribute to HF.
NSAIDs — Nonselective NSAID use is not associated with a first occurrence of heart failure (HF); however, it can cause a worsening of preexisting HF. The major mechanism for HF exacerbation is an increase in afterload resulting from NSAID-induced systemic vasoconstriction, which can lead to a further reduction in cardiac contractility and cardiac output in advanced HF. Data are more limited but there is a similar concern with the COX-2 selective agents. Several studies have presented data indicating that the selective COX-2 inhibitor, celecoxib, may have an improved cardiorenal safety profile compared with ibuprofen or diclofenac (nonselective NSAIDs) (12).
Glucocorticoids — Therapeutic use of glucocorticoids has been associated with dose-dependent increased rates of heart failure, myocardial infarction, stroke, and all-cause mortality (13). In a large observational study, the risk of heart failure appeared to increase with the daily dose of glucocorticoids prescribed, with a rate ratio of 3.72 (95% CI 2.71-5.12) with greater than or equal to 7.5 mg/day of prednisone or its equivalent compared with nonusers [14]. The cardiovascular risk was higher for those who had continuing prescriptions than for intermittent prescribing of glucocorticoids and higher for those using glucocorticoids during the six months prior to the cardiovascular event versus at an earlier time.
Targeted TNF-alpha inhibitor use may be associated with heart failure (HF). Concern about this possible adverse effect stems from randomized clinical trials of TNF-alpha inhibitors as a potential therapy for HF, and from postmarketing surveillance data gathered by the FDA. Clinical trials of both etanercept and infliximab were performed with the hypothesis that TNF-alpha inhibition would improve cardiac function in patients with HF [15-16].

Two major randomized, placebo-controlled trials evaluated etanercept as a possible therapy HF: the RENAISSANCE trial and the RECOVER trial [17-18]. Patients with New York Heart Association class II to IV chronic heart failure and a left ventricular ejection fraction less than 31 percent were enrolled. The two trials differed in the dose of etanercept used. The primary end point in both trials was clinical status at 24 weeks. In addition, analysis of the effect of the two higher doses of etanercept on the combined outcome of death or hospitalization due to chronic HF from the two studies was also planned.

In the combined analysis of these two trials (ie, RENEWAL), etanercept was found to have no effect on the death or chronic HF hospitalization end point. The relative risk for etanercept-treated patients was 1.1 (95% CI 0.9-1.3). On the basis of prespecified stopping rules, both trials were terminated prematurely because of futility. In addition to excluding any clinically relevant benefit of etanercept on the rate of death or hospitalization due to chronic HF, RENEWAL also raised concerns about the possible exacerbation of HF in some patients treated with TNF-alpha inhibitors.

These concerns were confirmed in a trial involving infliximab as a therapy for HF, known as the ATTACH trial (15). In this trial, the major inclusion criteria were New York Heart Association class III or IV HF and a left ventricular ejection fraction less than 35 percent. One hundred and fifty patients were divided into three treatment groups: placebo, infliximab 5 mg/kg, and infliximab 10 mg/kg. Infliximab was administered by intravenous infusion at weeks 0, 2 and 6. No infliximab was given after week six, and patients were followed for one year.

An analysis of all-cause mortality at one year showed that deaths were highest in the high-dose infliximab arm. There were eight deaths (16 percent) in the infliximab 10 mg/kg group, compared with four (8 percent) in both the infliximab 5 mg/kg and placebo groups

Given the evidence to date, in patients with symptomatic HF, it is suggested that treatment strategies other than TNF-alpha inhibitors should be employed. In a patient who develops HF while on a TNF-alpha inhibitor, a drug-induced cause should be suspected and use of the medication should be suspended.

For patients with RA and mild (NYHA functional class I or II) HF whose arthritis is refractory to other DMARDs or biologic agents, targeted TNF-alpha inhibition might be considered.

Cyclophosphamide is related to many adverse reactions such as marrow suppression, susceptibility to infections, sterility and amenorrhea, as well as nephrotoxicity and cystitis, and most importantly cardiovascular complications, for instance, sinus bradycardia, pericarditis, myocarditis and heart failure. More studies need to be conducted in order to determine the eventual indication of cyclophosphamide in patients with heart failure with RA.

Conclusion:

- The risk of developing heart failure (HF) is increased in patients with RA. The prevalence of echocardiographically determined LV systolic and both left and right ventricular diastolic dysfunction is also increased in this population.
- RA itself appears to be an independent risk factor beside established risk factors (eg, hypertension, diabetes, dyslipidemia)
- The differential diagnosis of HF in patients with RA includes interstitial lung disease and pericardial disorders.
- Antiinflammatory and anti-rheumatic drug therapy may play a role in precipitating or exacerbating HF. These include: anti-TNF agents, NSAIDs, COX-2 selective inhibitors, antimalarial drugs, and glucocorticoids.
- Primary prevention of HF in RA patients is based on modifying traditional risk factors for HF, for ischemic heart disease, and optimizing control of RA disease activity.
- Echocardiography should be performed in patients with RA who have abnormalities on history, physical examination and/or ECG that are suggestive of LV dysfunction.
- Treatment of HF is similar in patients with and without RA, but attention to the possible adverse cardiovascular effects of antiinflammatory and anti-rheumatic drug therapy may lead to additional diagnostic studies, such as endomyocardial biopsy and/or cessation or gradual withdrawal of certain agents, particularly NSAIDs, COX-2 selective inhibitors, and glucocorticoids.

Figure 1: Chest X-RAY

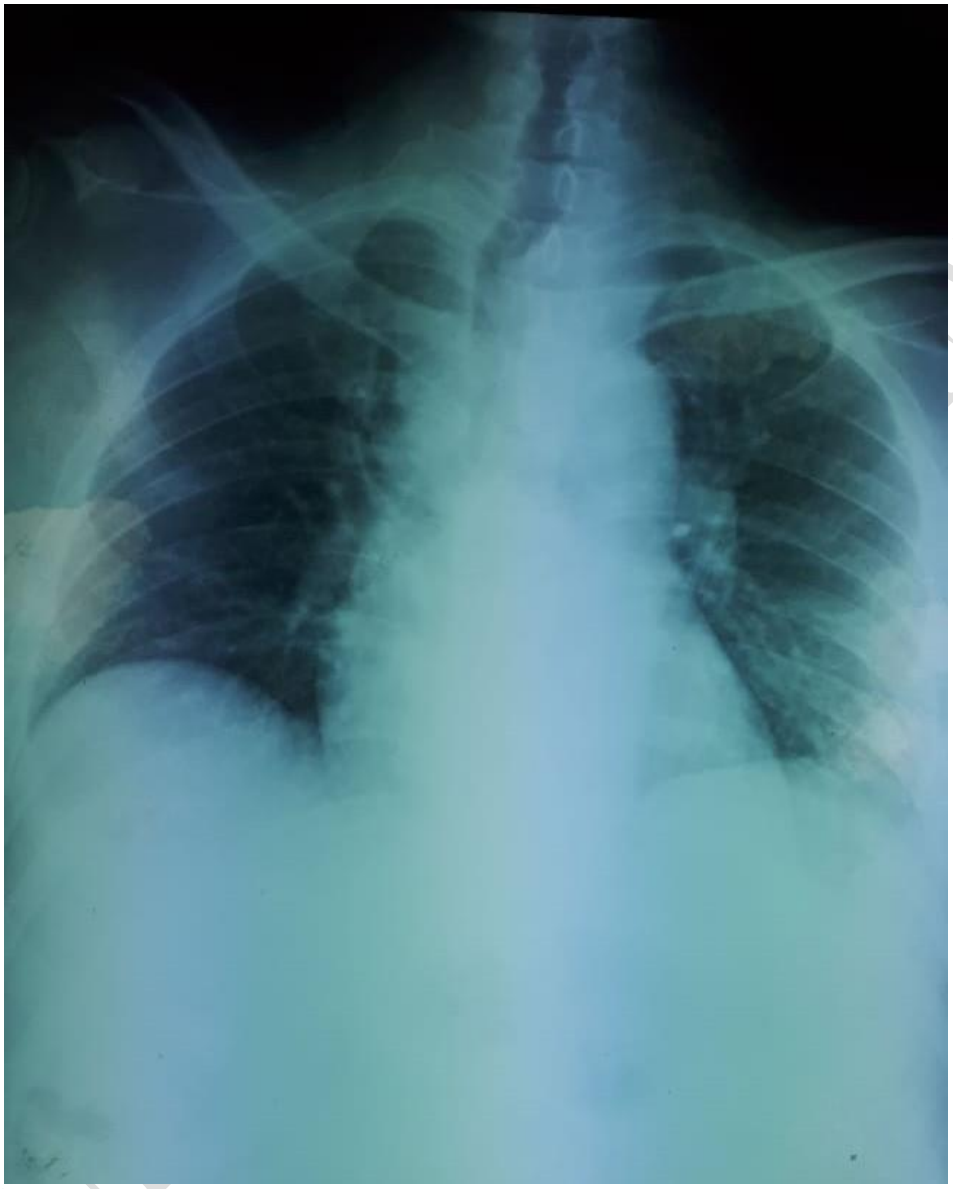


Figure 2 : echocardiography : global hypokinetic dilated cardiomyopathy with an ejection fraction of 15–20%, with apical thrombus

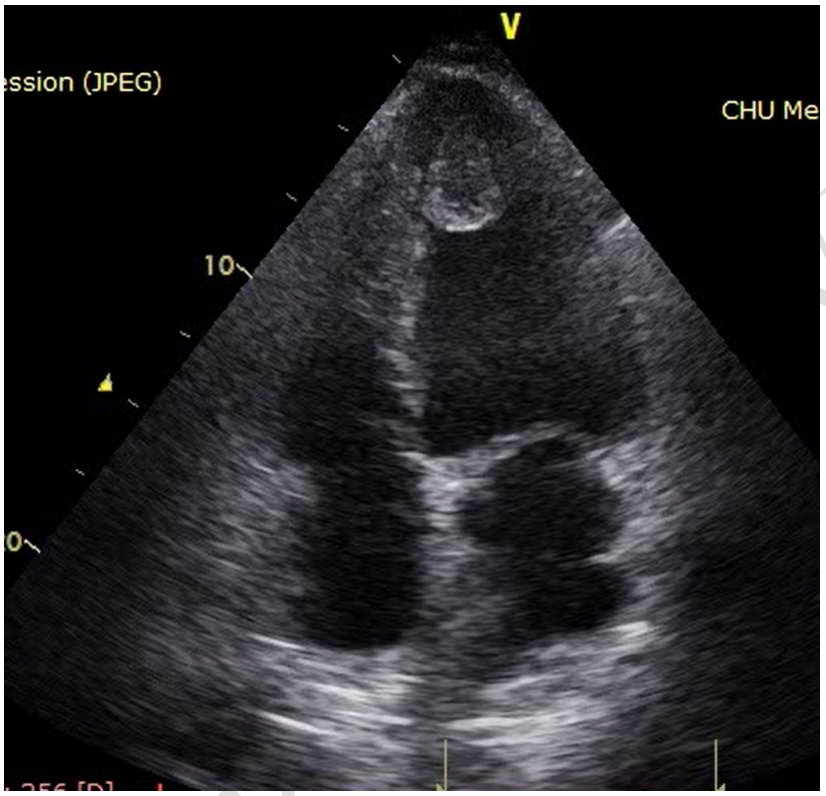
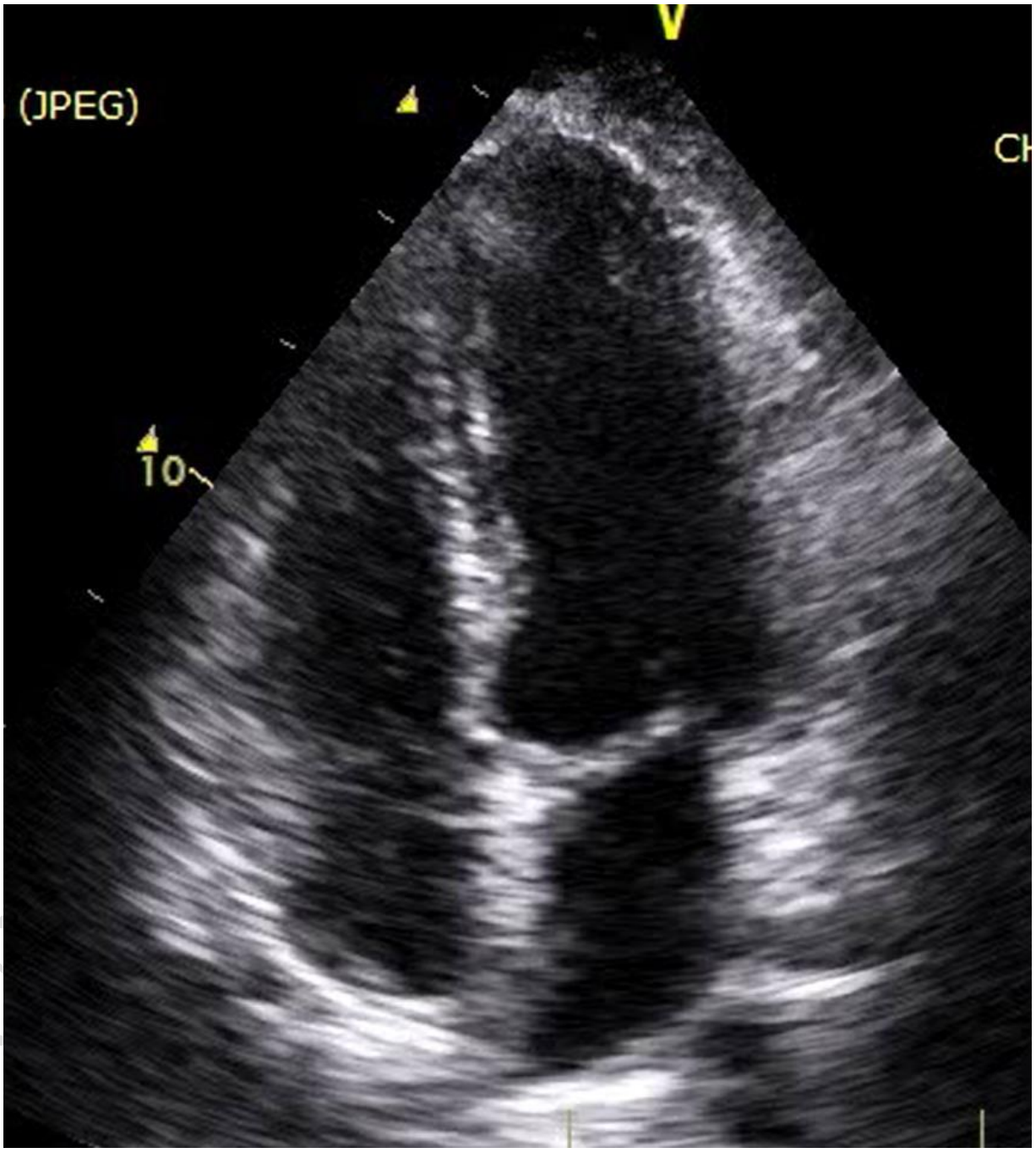


Figure 3: left ventricular ejection fraction >50% without thrombus



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