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CHEST COMPUTED TOMOGRAPHY FINDINGS IN FEBRILE PATIENTS WITH HEMATOLOGICAL MALIGNANCIES

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ABSTRACT

Background: Pulmonary complications, infectious or non-infectious, are very common complications in patients with hematological malignancy. This study addresses the role of computed tomography (CT) scan in assisting in the diagnosis of pulmonary complications in those patients. **Patients and method:** This is a prospective study, performed in Baghdad teaching hospital, Medical city, Baghdad, Iraq where 50 patients with and 50 patients without hematological malignancy presented with fever of unknown cause at time of admission in the period from April 2017 to February 2018. Chest CT scan was performed for every patient and the findings were compared between the two groups. **Results:** There was no statistical difference between the two groups regarding the site, distribution or pattern of any intrapulmonary lesion, Bacterial pneumonia is the most common cause of pulmonary lesions followed by fungal infection in patients with hematological malignancy, compared to Bacterial pneumonia then tuberculosis in patients without hematological malignancy. Specific signs found in CT scan (Halo sign , Reverse halo sign, Tree in Bud sign) are more likely to be encountered in patients with hematological malignancy (66% versus 33%, P-value 0.032). **Conclusion:** There is no difference in distribution or pattern of imaging findings. The most common cause of CT scan lesions in both groups is bacterial infections. CT scan, intertwined with the clinical data of the patients, proves to be a valuable tool in reaching the final diagnosis especially in those with fever, and may assist in the early detection, assessing of severity, and treatment response of those complications, hopefully decreasing mortality and morbidity.

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INTRODUCTION

Hematological malignancies or tumors of hematopoietic and lymphoid tissue are tumors that affect the blood, bone marrow, lymph and lymphatic system, since these elements are closely related through the circulatory (vascular and lymphatic) and immune systems, a disease affecting one of them usually affects the others as well making them an overlapping problem (Vardiman, 2009). It is well known that cancer, diagnosed or undiagnosed, can cause fever, this of course can be due to the tumor itself or due to complications caused by infection and non -infectious complications (Cunha, 2004).

Pulmonary complications in hematological malignancy can be divided into:

Noninfectious complications (like pulmonary hemorrhage, pulmonary edema, Pulmonary leukostasis) (Tanka, 2002). Infectious complications (including bacterial infections - neutropenia is the major predisposing factor for bacterial infections, or fungal infections - the most common fungal infection is aspergillosis) (Franquet, 2009). Aspergillosis is the most common fungal infection in hematological malignancy & can present with the following CT signs:

Halo sign: is a nodule or mass surrounded by ground glass opacity represents hemorrhage, this sign is only seen within the first 10 days of angioinvasion after which it disappears (Figure 1) (Greene, 2007).

Air crescent sign: it represents a nodular opacity with retracted infarcted lung with crescent and circular cavitation & is seen in 50% cases, usually after two weeks of disease onset

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& is non-specific & can be seen in bacterial pneumonia, focal lung injury, interstitial lung disease & lung granulomatosis (Figure 2 & 3) (Gotway, 2002).

Hypodense sign: appears as a relative hypodensity within a nodular lesion. It has low sensitivity but with high specificity (Horger, 2005).

Reverse halo sign (atoll sign): represents central ground glass opacity surrounded by denser ring like consolidation, it is most commonly associated with mucormycosis in neutropenic patients (Figure 1) (Godoy, 2012). Candidiasis is also a common cause of fungal infections in hematological malignancy and produces the patches of consolidation and cavitation of pulmonary nodules on CT Scan (Franquet, 2006). Pulmonary mucormycosis is an opportunistic pulmonary infection from fungus belonging to the order Mucorales. It should be differentiated from invasive pulmonary aspergillosis (Bennet, 2014), on CT, it may appear as ground glass opacities (Georgiadou, 2011) or the reverse halo sign (Kligerman, 2013) has been considered as a good specific sign that suggest mucormycosis with correlation with clinical settings (12). Viral pneumonia: most commonly Cytomegalovirus, other causes of viral pneumonia include: Rhinoviri, Adenoviri, Influenza virus, Parainfluenza virus, Respiratory syncytial Virus (Franquet, 2006). Workup in febrile patients with hematological malignancy: Of course, definitive diagnosis requires histological and/or culture evidence from tissue biopsies or resection material or positive cultures from normally sterile body fluids (pleural fluids), however, these criteria may not be applicable, especially at early stages of infection and most of the times starting therapy for these pulmonary complications is mostly based on clinical criteria such as: antibiotics refractory fever or pulmonary symptoms with detection of pulmonary infiltrates by chest X-ray, and/or Computed tomography (Ruhnke,2011). The radiologist's role is to guide the clinician towards a specific diagnosis such as: Aspergillus, pneumocystis, or point them towards noninfectious causes: tumor localization, hypervolemia, bronchitis obliterans, drug toxicity or embolism (15). CT Scanning has been shown to be superior to standard X Ray imaging in identifying, localization and spread of lesions as well as for assessment of aetiology, CT is currently recommended when there is suspicion of an infectious chest complication in patients with hematological oncology (16). The aim of this study is to evaluate chest CT findings in febrile patients with hematologic malignancy & compare them with those in febrile patients with no such malignancy.

PATIENTS AND METHODS

This is a prospective randomized controlled study, performed in Baghdad teaching hospital, Baghdad, Iraq, in the period from April 2017 to February 2018. Our study sample consist of two groups, (each group consist of fifty adult patients), presented with fever of unknown cause, the first group (termed as group one) were patients with hematological malignancy, while the second group (termed as group two) were patients without hematological malignancy. Each patient was informed about the nature, the goal of the study, and the risks of ionizing radiation exposure, and risks associated with intravenous iodinated contrast injection. An informed written consent was taken. Chest x ray was performed initially for each patient. Patients taking oral metformin are requested to stop it 2 days before and following intravenous contrast. Then a native chest CT scan was done, if it was normal, no further imaging study is performed, but if it was abnormal, then the need intravenous contrast was assessed. The contrast used was Omnipaque (dose of 1 ml/Kg of 350 mg/100 ml concentration) was administered intravenously by an injector in flow rate of 2.5 – 3 ml /second, another scan was done after 30 seconds. The equipments used in the study were multidetector CT Philips Brilliance (64 slices) and Toshiba Acquilion (128 slices) using the following parameters tube voltage 120 kVp with tube current-time product setting ranging from 80 -300 mAs. Images were interpreted on a workstation using different windows (mediastinal, pulmonary & bone windows), and the data were recorded on the data sheets. All patients were admitted for follow up. Final diagnosis was reached by performing cytological tests (sputum and / or pleural aspirate for cytology or culture and sensitivity) or histological tests (Excisional or incisional biopsy) in some patients or by the patients' response to treatment.

RESULTS

Mean age of patients in group two was significantly higher than those of group one, while the distribution of gender was not statistically different between the two groups (Table 1).

Table 1. Age and Gender

	No hematological malignancy	Hematological malignancy	P value
Number	50	50	-
Age	49.5 ± 18.2	42.1 ± 18.0	0.037
Gender			0.100
Female	21 (42.0%)	29 (58.0%)	
Male	29 (58.0%)	21 (42.0%)	
Independent t test			
Chi square test			

Table 2. Specific signs finding

Non Hematological condition	Hematological condition	OR (95%CI)	P value
10 (33.3%)	20 (66.7%)	2.667 (1.090 – 6.524)	0.032
OR: odd ratio, CI: confidence interval			

There was no statistical difference in the lobar distribution of the pulmonary lesions, the pattern of intrapulmonary opacification/consolidation, the incidence & distrubution of pulmonary collapse, in the distribution of interstitial abnormality (including tree-in-bud, reticulonodular, linear-interstitial, fibrotic band, septal thickening patterns), in the distribution of nodular opacity, in the distribution of pulmonary cysts or cavities, in the distribution of pulmonary bronchial abnormality & in pleural findings between the two groups. There were 3 patients with ring like consolidation with central ground glass opacification (reverse halo sign) indicating mucormycosis infection and all of whom were in patients with hematological malignancy (Figure 1) One patient with miliary TB was encountered, and he didn't have a hematological malignancy, other nodules (single, multiple or micronodules) were found evenly distributed in both groups. There was significant difference in the presence of malignant looking lymph nodes between the two groups. 40% of malignant looking lymph nodes are with NHL patients, and 30%are with HL patients, 30% are with AML, furthermore, in our sample 37.5% of patients with HL have malignant looking mediastinal lymph node(s), and 30.7% of patients with NHL

Table 3. Final diagnosis in patients with and patients without Hematological malignancies

	Non Hematological malignancy	Hematological malignancy
Bacterial	18 (36.0%)	21 (42.0%)
Fungal	0 (0.0%)	9 (18.0%)
Non specific	0 (0.0%)	2 (4.0%)
Viral	2 (4.0%)	0 (0.0%)
TB	10 (20.0%)	1 (2.0%)
Noninfectious	0 (0.0%)	7 (14.0%)
Malignancy	6 (12.0%)	0 (0.0%)
Relapse	0 (0.0%)	2 (4.0%)

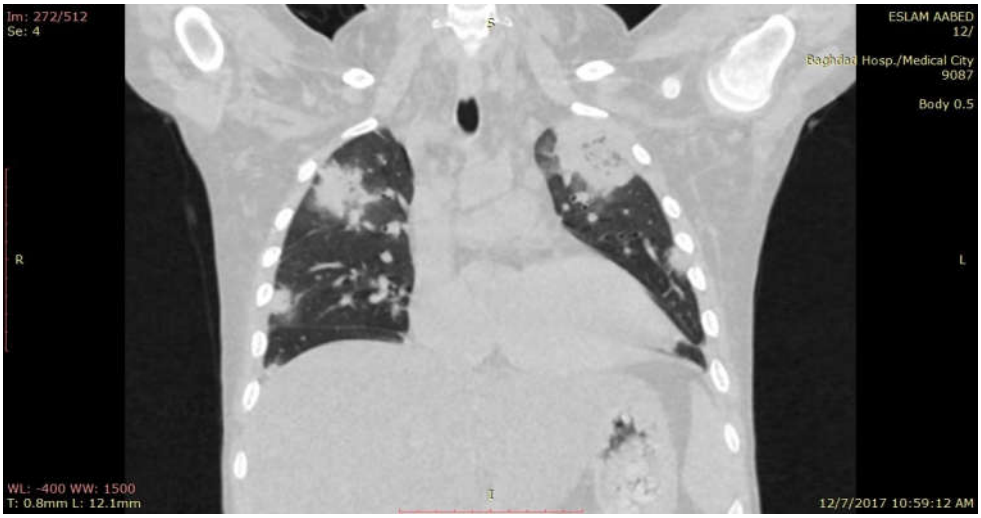

Figure 1. Coronal CT image of a 20 year old man managed for acute lymphoblastic leukemia, showing reverse Halo sign in the upper left lobe and multiple lesions with Halo sign

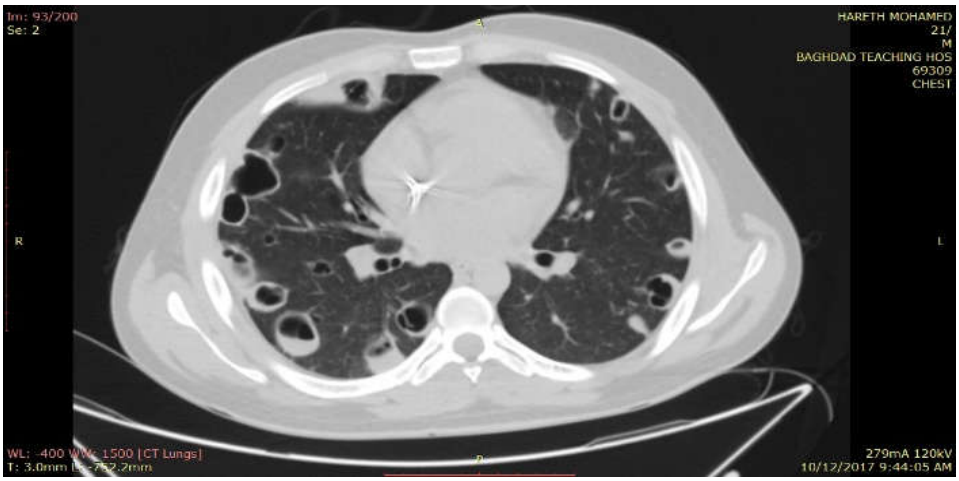

Figure 2. Axial CT scan of 18 year-old male with Hodgkin's lymphoma showing diffuse cavitary lesions diagnosed as fungal infection

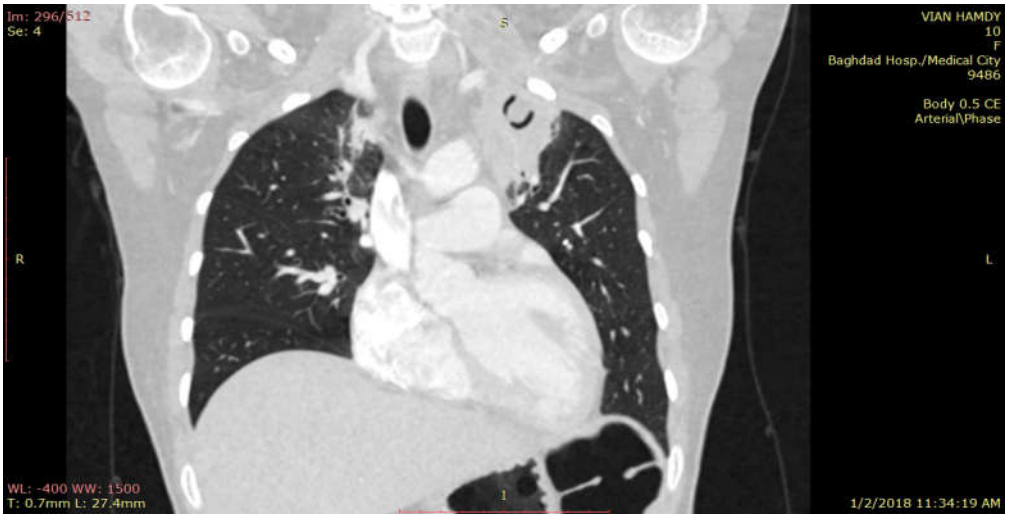

Figure 3. Coronal CT image of a 28 year-old female with acute myeloid leukemia, showing left upper lobe mass like consolidation with air crescent sign, final diagnosis was fungal infection

have malignant looking lymph node enlargement. Specific signs (including halo sign, reversed halo sign, tree-in-bud opacities) are 2.667 folds associated with hematological conditions ranging from 1.09 to 6.5 folds, and it was statistically significant (Table 2). Most of the patients in both groups were found to have bacterial infection, while fungal infection was found only in hematological patients. There were 2 non-specific patients who had no specific CT scan finding that didn't lead to a definitive diagnosis, and were ultimately treated with broad spectrum antibacterial, antifungal, antiviral without histopathological diagnosis, Non-infectious complications include (leukostasis and reactionary pleura effusion) (Table 3) Most patients with pneumonia in both groups (whether bacterial, fungal, or even Viral) had consolidation as the primary finding in CT, however; in hematological malignancy, it is more likely associated with other CT scan findings like pleural effusion. It also noted that consolidation in hematological patients are mostly bacterial and fungal (23% each), and in non-hematological patients are mostly bacterial and TB infection.

DISCUSSION

Febrile patients suffering from hematological disease (myeloid leukemia, lymphoid leukemia, lymphoma, multiple myeloma, plasma cell disorders, etc) have a bad prognosis if the cause of their fever was not detected as early as possible (Uhrmeister, 1992). Chest radiograph remains the initial radiographic investigation in immunocompetent patients with chest infection, but in immunocompromised patients CT scan is more sensitive than conventional X-ray due to the possibility of atypical infections like mycoplasma, fungal infection or the presence of non-infectious complications (Reynolds, 2012). In this study, febrile patients tend to be younger if they have a hematological condition (Mean age 42.1 years in hematological patients compared to 49.5 years for the immunocompetent group with a p-value 0.037), this can be explained by the fact that any infection that is an indication for hospital admission mostly afflict people who are in extreme age groups or who are younger and immunocompromised (Reynolds, 2010), and since pediatric age group were not included in this study, most of the immunocompetent patients in the current study are older than their immunocompromised counterparts. In this study, there was no specific pattern or distribution difference of any intrapulmonary lesion regarding their hematological condition, and this is compatible with other studies like that of Xiangpeng Zheng in 2014 which stated no specific site or distribution difference between patients with and patients without hematological malignancy (20), and the results of Escuissato and Warszawiak (Escuissato, 2014) who mentioned no particular pattern that is special in hematological malignancy patients.

There was no statistical difference between our two groups regarding the rate and the distribution by which atelectasis occur, however; 38% of patients in group one diagnosed with bacterial pneumonia, were found to have an associated collapse, this is against (16.7%) in patients in group two with bacterial pneumonia. In patients with no hematological malignancy Tuberculosis was mostly associated with collapse (70%). There was no statistical difference between the two groups regarding interstitial opacification which is in accordance with a study done by Mehmet SB *et al* (Mehmet, 2012). This can be attributed to the fact that the radiologically observed interstitial opacification in patients with fever is usually caused by infective agents rather than an interstitial lung diseases**.** In this study, 46% of nodular opacification found in non-hematology patients are caused by malignancy (primary or secondary lung cancer) followed by TB in 36 %, while in hematological malignancy patients 66% of nodules is caused by infectious complications, 33% bacterial and 33% fungal, keeping in mind that malignant nodules are larger and are speculated while infections mostly present with micronodules, or nodules surrounded by ground glass (Halo sign) (Figure 2). These correlates with Wingard JR results published in 2012 (Wingard, 2012). There were no significant difference in the rate of occurrence of cavitary lesions between the tow groups. But the causes differ between the two groups (image 3); There were three immunocompetent patients with cavitary lesions, (2 were diagnosed as having lung malignancy and one diagnosed as TB), while hematological patients with cavitary lesions were six, (3 of them were diagnosed with bacterial pneumonia and the other three were diagnosed with fungal pulmonary infection), this difference in the cause between the two groups can be explained by the fact that patients with hematological malignancy are immunosuppressed so morphological appearances of pulmonary infections are different from that of immunocompetent patients (Curtis, 1979). Invasive pulmonary aspergillosis affects severely immune compromised patients especially those with hematological malignancy, cavitation generally emerge later in the course of the disease (Gefter, 1985).

Regarding Bacterial pneumonia and cavitation in immunosuppression there is a higher chance of developing necrotizing pneumonia, or lung abscesses, this is usually caused by H. Influenza or S. pneumoniae (Beth, 2018). Bronchial wall thickening is mostly found in infection, inflammation like asthma, pulmonary edema and other diseases (Bramson, 2005), no significant difference was found between the two groups, all patients with bronchial wall thickening in both groups were found to have bacterial bronchitis.In this study, only 4% of the hematology patients with fever were found to have inflammatory lymphadenopathy compared to 8% in non-hematology patients the rest of the patients were found to have malignant appearing lymphadenopathy most of them are lymphoma patients (40% in NHL patients, and 30% in HL patients, 30% are with AML). In the current study, 5 patients (10%) with hematological malignancy were found to have pericardial effusion (2 have AML, 1 have Hodgkin's, 1 have Non-Hodgkin's lymphoma and 1 have CML). Causes of pericardial effusion in hematological malignancy could be due to: direct involvement of the pericardium by the malignant process, as a reaction to treatment (chemotherapy, mediastinal radiation, or even in Graft Versus Host Disease in patients with bone marrow transplantation), or due to infectious complications (Gornik, 2005), higher percentage of pericardial effusion found in other studies, as Keeran S. *et al* mentioned that 20% of patients with leukemia has pericardial effusion (Keeran, 2010), Acquatella GC and colleagues stated that 53% of patients with NHL, develop pericardial effusion (Acquatella, 1982), while Adler AC and Cestro C mentioned that 5% of patients with HL had pericardial effusion (Adler, 2012). This difference can be explained by using echocardiography in these studies, which is more sensitive than CT used in our study. In this study, two patients in group one diagnosed with pleural thickening (one had fungal infection) and it is not certain whether his pleural condition was due to secondary pleural lymphoma or due to

extension of infection to the pleura as most of hematology patients are treated with broad spectrum antibiotics and antifungal without cytology or histopathology confirmation of their final diagnosis. Three patients in group two were found to have pleural thickening: (one was found to have metastatic carcinoma, the other was diagnosed as mesothelioma after pleural biopsy, the last patient was diagnosed with TB). Pleural effusion is a common finding in hematologic malignancy, it may be due to direct involvement by the neoplastic process, as a side effect of treatment or due infectious causes (Alexandrakis, 2004), and it was found in 38% of paitents with hematological malignancy (the cause being divided to parapneumonic (16 cases) and reactionary pleural effusion (3 cases). It is comparable to the results of Alexandrakis and colleagues (32). Non-hematology patients with pleural effusion were totally 14 patients, (6 had bacterial pneumonia, 5 cases of TB, 2 cases with H1N1 influenza infection and one case with cancer of unknown origin. 47.5% of cases with pneumonia has pleural effusion (para-pneumonic pleural effusion), 6.8% of them had empyema, these results match that mentioned in a large study by Light RW and colleagues who found that the percentage of patients with chest infection of any type who had pleural effusion was 20-57%, 5-10% of them had empyema (Strange, 1999).

In this study, specific CT scan signs (e.g. Halo sign, reverse halo sign, tree in bud opacification, etc.) was found significantly more common in patients with hematological malignancy (66.7% versus 33.3%, p-value= 0.032). which indicate that chest CT scan is very informative and can actually help to determine the final diagnosis in patients with hematological malignancy and fever. In this study, 36% of patients with no hematological malignancy and 42% of patients with hematological malignancy have bacterial pneumonia, it usually present with consolidation with air bronchogram, and in this study, accompanying pleural effusion was much more common in association with bacterial pneumonia in hematological malignancy patients (found in 71.4% (n=15) in hematologic patients (Table 17), while it was encountered in 22.2% (n=4) in non-hematology patients with bacterial pneumonia. Mediastinal lymphadenopathy is more commonly encountered in hematologic patients which could be either of infectious etiology or neoplastic proliferation, Boomart *et al* mentioned the same kind of spectrum of presentations of Bacterial pneumonia in hematology patients (34)(Image 9). In this study, 18% of febrile patients with hematological malignancy were found to have fungal lung infection while no immunocompetent patient where found to have this complication, additionally, most common causes of consolidation in hematology patients were caused by bacterial infection (62%) followed by fungal infection (26%), while in non hematology patients bacterial was the cause in the same percentage (62%), while the second most common cause was TB (24%), which approximate the results found in a study by Boch T. *et al* (35), who found the percentage of patients with proven or probable diagnosis of invasive fungal disease was 37.3%. Besides consolidation, fungal infection can present with cavitary lesions (Figure 2), nodular opacification among others, specific signs were common among pulmonary fungal infection patients like Halo, reverse halo signs (Greene, 2007 and Godoy, 2012). In the current study, only one patient (2%) had a proved tuberculosis, which is comparable to the results of a study performed by Silva FA (Silva, 2005) who found an incidence of 2.6% Non-infectious complications were mostly pleural effusion reactionary to chemotherapy, LAP due to the disease itself, infiltrative pulmonary lymphoma in one patient, and one (Image 12), who was a 30 year-old man with AML, presented with fever, dyspnea and WBC count of 110,000 cells/mm3, his CT scan showed multiple non enhancing peripheral wedge shaped opacities, with bilateral pleural effusion, with basal consolidation, his CT angiogram showed no main pulmonary artery or its major branches filling defect with multiple peripheral segmental branches filling defect (blockage).

Conclusion

There is no difference in distribution or pattern of most imaging findings. The most common cause of CT scan abnormality in both groups is bacterial infections, followed by fungal infections (in hematological patients), followed by non-infectious pulmonary complications. Patients with hematological malignancy have higher incidence of associated thoracic features especially pleural effusion and lymph node enlargement. Clinical data combined with an expert interpretation of chest CT proved to be a valuable tool in reaching the final diagnosis especially in febrile patients.

Abbreviations

ALL Acute lymphoblastic leukemia
AML Acute Myeloid Leukemia
CLL Chronic Lymphocytic Leukemia
CML Chronic Myeloid Leukemia
CT Computerized Tomography
HL Hodgkin's Lymphoma
NHL Non-Hodgkin's Lymphoma
TB Tuberculosis

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