Pancytopenia a Three Years Evaluation

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Abstract: Background: Pancytopenia is an important clinico-hematological entity encountered in our day to day practice from a number of disease processes primarily and secondarily involving bone marrow (1,2). The severity of pancytopenia and the underlying pathology determine the management and prognosis of the patients (3). The present study has been undertaken to evaluate the various causes and to correlate the peripheral blood findings with bone marrow aspirate which helps in the treatment(4). The objective is to study pancytopenia due to various causes and to evaluate hematological parameters. Methodology is retrospective study of 106 cases of pancytopenia on clinical and hematological parameters was done in the department of pathology, RIMS Medical college kadapa, AP, India during November 2011 to October 2014. The result of 106 cases showed the commonest physical finding was pallor and megaloblastic anaemia was the predominant hematological picture. Bone marrow evaluation is conclusive in all cases. The present study concludes that detailed primary hematological investigations along with bone marrow evaluation are helpful for the understanding of the disease process and to diagnose or to rule out the causes of pancytopenia and to plan for further investigations and management.

Keywords: Pancytopenia, megaloblastic, Aplastic, anaemia, bone marrow

1. Introduction

Blood counts are low due to premature destruction in reticuloendothelial system and removal of cells from the circulation or inadequate production in the body. Pancytopenia is a reduction in erythrocytes, leucocytes and platelets. As such it is not a disease but three disease processes which primarily or secondarily affect the bone marrow (2). It is one of the important feature of many serious and life threatening illnesses (5). The pattern of diseases leading to pancytopenia is expected to vary in different population with their differences in age pattern, nutritional status and prevalence of infective disorders (4). The Presenting symptoms are usually due to anaemia or thrombocytopenia but the symptoms due to leucopenia can become most serious threat to life during the subsequent course of the disorder (6). Haematopoietic tissue is one of the rapidly proliferating tissue in the body in which DNA synthesis is rapid, cyanocobalamin and folate are essential for DNA synthesis and deficiency of either or both causes a failure of DNA synthesis and disordered cell proliferation. The most important and difficult choice of diagnosis in the pancytopenic patients rest among primary bone marrow disease. The severity of pancytopenia and the underlying pathology determine the management and prognosis of these patients. Prompt recognition of the conditions is essential for effective management; otherwise the condition may become fatal. An attempt is made to evaluate the causes of pancytopenia.

2. Review of Literature

Causes of Pancytopenia (7)

1. Bone marrow disorders:
   a) Aplastic anaemia
   b) Myelodysplasia
   c) Acute leukemia
   d) Myelofibrosis
   e) Infiltrative diseases - lymphoma, myeloma, carcinoma, hairy cell leukemia

   f) Megaloblastic anaemia

2. Non marrow disorders
   a) Hypersplenism
   b) Systemic lupus erythematosus
   c) Infections-TB, AIDS, Leishmaniasis, Brucellosis

APLASTIC ANAEMIA: Erlich in 1888 attributed Aplastic anaemia to primary depression of marrow function. Thompson w.p. al in 1934(8) described Aplastic anaemia as a distinct clinical entity characterised by pancytopenia thought to be the result of depressed bone marrow activity. In editorial hypothesis by Doggs D.R. et al (9) stated that Aplastic anaemia is an idiopathic disease in which no cause for marrow insult can be identified.

FAMILIAL APLASTIC ANEMIA: Fanconis’s anaemia was first described by Fanconi in 1927 in three brothers with pancytopenia combined with physical abnormalities. Ueshlinger then reported in 1930 a similar patient with aplastic anaemia and abnormalities of the thumb and kidney. Fanconi indicated and Naegeli suggested in 1931 that familial aplastic anaemia plus congenital anomalies be called Fanconi’s anaemia.

DRUG INDUCED APLASTIC ANAEMIA: Chloramphenicol is frequently implicated as a cause of bone marrow aplasia. An analysis of 408 cases chloramphenicol associated, non neoplastic depression of blood elements by Naga,T. et al in 1969 concluded that people of all ages are affected a broad age spectrum ranging from 25 to 65 years old for adults and in childhood. Nevertheless, it is still used inappropriately perhaps in part because there is a common belief that parenteral form has not been associated with aplastic anaemia as stated y Glickmann R. A in 1975. But Alavi J.B. in 1983(10) reported a case of aplastic anaemia associated with intravenous chloramphenicol. In wallerstein’s study in 1969, one patient was exposed to intramuscular chloramphenicol only 9 months before developing pancytopenia. The patient reported by Grilliat et al., in 1981 received intravenous chloramphenicol for 22 days and developed aplastic anaemia 6 weeks later.

Volume 4 Issue 12, December 2015

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Although a number of drugs belonging to NSAIDS have been reported to be associated with aplastic anemia, phenylbutazone has been most closely associated with this disorder. Mc Carthy DD et al in 1964(11) reported in his study, the association of phenylbutazone with aplastic anaemia. Robbins MM et al in 1962 reported more than 50 cases of aplastic anaemia associated with anticonvulsant therapy especially methylphenylethyl hydantoin and trimethadione. At one time gold compounds were popular for the treatment of rheumatoid arthritis and to a lesser extent of Lupus erythematosus and tuberculosis. In one series studied by Fitzpartrick W.J. et al in 1948 fatality rate in patients with aplastic anaemia associated with gold use was high. Organic arsenicals, once the agents of choice in the treatment of syphilis are known to cause a variety of blood dyscrasias including aplastic anaemia as reported by Freeman H.E. in 1944.

Hagler, L et al in 1975(12) sated the increasing frequency of association of aplastic anaemia with viral illnesses especially infectious hepatitis. An association between viral hepatitis and aplastic anaemia was first reported in 1955 by Lovenz, E. et al. Hagler, L et al in 1975(12) described more than 200 cases where aplastic anaemia occurred typically within six months of the onset of hepatitis. Spivale J.L. et al in 1984(13) evaluated bone marrow in AIDS patients with high incidence of meyloloblastic, pancytopenia and alterations in marrow cellularity.

Hematologic abnormalities in miliary tuberculosis are well recognised. The anaemia of chronic disorders is frequently found, so also leukopenia and thrombocytopenia. Bindu R.S et al in 2000(14) have evaluated 38 cases of Pancytopenia and observed that 5.5% of cases of miliary tuberculosis were associated with pancytopenia.

O Brien HA et al in 1991(15) reported an unusual case of megaloblastic anaemia with marked erythroid hypoplasia and myeloid hyperplasia. The serum cobalamin and unsaturated cobalamin binding capacity were both grossly elevated. This patient responded well to folate therapy, Tilak V &Jain R in 1999(3) studied 77 cases of pancytopenia and observed that megaloblastic anaemia and aplastic anaemia were the major causes of pancytopenia. They suggested that bone marrow examination could be deferred in those cases presenting with hepatosplenomegaly and hypersegmented neutrophils in the peripheral smear. These patients could be put on haematinics with close hematological follow up.

Bretnach et al in 1981(16) observed transient pancytopenia prior to the onset of acute lymphoblastic leukaemia in children and concluded pre leukemia aplasia in childhood is a feature of ALL. In a review of 869 case of multiple myeloma by mayo clinic in 1975 observed pancytopenia at the time of presentation in less than 20% of patients but frequently evolve during the course of the disease.

There is considerable variation in the incidence of bone marrow metastasis for different types of malignant neoplasms. These include carcinomas of the breast, prostate, lung and gastrointestinal tract in adults and neuroblastomas in children( Anner RM et al 1979). Acute myelofibrosis was first described by Lewis and Szur in 1963. In a study conducted by Das, S et al in 1997(17) of an acute myelofibrosis 2 out of 5 cases presented with pancytopenia. Brenner, B et al in 1985(18) encountered pancytopenia associated with marrow fibrosis in a patient with Angioimmunoblastic lymphadenopathy. Devi k et al in 2000(19) reported four cases of bone marrow necrosis and all of them presented with peripheral blood picture of pancytopenia.

3. Problem Definition

Pancytopenia is an important hematological sign seen in many diseases directly or indirectly involving the bone marrow. It should be thoroughly investigated before treating the patients.

4. Methods/Approach

A retrospective study of pancytopenia was carried out in the department of pathology RIMS medical college, kadapa from November 2011 to October 2014. A total number of 1050 cases were studied particularly with reference to predisposing factors (20).The patients studied were admitted to medical, surgical, pediatric, orthopedic and gynecology wards with various complaints. Out of these 106 patients showed pancytopenia were taken for the study. Pancytopenia cases were selected based on hemoglobin, total count, platelet count and peripheral smear examination. Presence of hemoglobin less than 9 gm/dl, total leucocyte count less than 4000/cumm and platelet count less than 140,000/-cumm are taken as criteria for pancytopenia. Both sexes and all ages are considered. Bone marrow aspiration was done in 104 cases from posterior iliac crest and sternum. Two of the patients were not under gone the procedure. Peripheral blood and bone marrow aspiration smears are stained with leishman stain. Bone marrow biopsy was done from the posterior iliac crest. Trephine sections are stained with haematoxylin and eosin.

5. Results/Discussion

Out of these 1050 patients, 106 cases with pancytopenia were seen over 36 months forming 10.09%. They consisted of 60 males and 46 females with 1.12:1 ratio and age ranging 4-75 years. Bone marrow aspiration was done in 104 patients but in 28 cases diagnosis was inconclusive. In those cases, bone marrow biopsy was done. Two patients did not under gone bone marrow procedure. In them, supplementation of haematinics done, based on peripheral smear findings . Reticulocyte count rise was observed after 5 days of haematinics therapy.

The causes of pancytopenia in 106 patients are megaloblastic anaemia 28 (26.42%)cases, hypersplenism 26(24.53%) cases, aplastic anaemia 14(13.20%) cases, dimorphic anaemia 8 (7.55%) cases, chronic inflammation 8 (7.55%) cases, subleukemic leukaemia 8(7.55%) cases, 4(3.77%)cases of micronormoblastic erythroid hyperplasia(unexplained cause), 4(3.77%) cases of non Hodgkins lymphoma, 4(3.77%) cases of multiple myeloma and 2 (1.89%) cases of tuberculosis.

Volume 4 Issue 12, December 2015
The commonest mode of presentation was generalized weakness and pallor 106(100%) cases. Other main symptoms were dyspnoea 45(42.45%) cases, fever 40(37.73%) cases, Splenomegaly38(35.85%) cases and hepatomegaly30(28.30%) cases. Bony tenderness was seen in multiple myeloma. Lymphadenopathy was seen in subleukemic leukaemia.

IN MEGALOBLASTIC ANAEMIA Males consists 17 cases and Females 11 cases. Age range is 05-40 years. All patients presented with symptoms of anaemia. There was mild splenomegaly in three cases and clinically mild icterus in six patients. There was unconjugged hyper bilirubinaemia in all six patients with mild icterus (range 1.5 mg/dl to 3.5 mg/dl). Three patients had clinical neurological deficits, of these subacute combined degeneration in two and sensory ataxia in one patient. Since Vit B12 and folic acid levels could not be estimated, both folic acid and parenteral hydroxyocobalamin are administered to all. All patients showed complete clinical and hematological remission. Figure 1.

IN HYPERSPLENISM, out of 26 cases males were 18 and females were 8. Age range is 13 to 49 years. The average time from onset of symptoms to diagnosis was 3 months. 12 patients presented with pain and mass in the abdomen, 6 patients presented with fever and 8 patients presented with weakness and fatigue. In all cases splenomegaly was detected clinically. In 12 cases splenomegaly was massive and in 14 cases moderate. 2 cases of massive splenomegaly and 10 cases of moderate splenomegaly were due to portal hypertension. In 4 cases malaria parasite was detected in peripheral smear and four cases are positive for QBC Figure2(d).

IN APLASTIC ANAEMIA male to female ratio is 8:6. Age range is 10-38 years. The average time from onset of symptoms to diagnosis was two months. Aplastic anaemia was mild in four, moderate in eight and severe in two cases. All patients presented with weakness, easy fatigability, lassitude and dyspnoea on exertion. Four patients presented with epistaxis and bleeding gums. No etiological factor could be implicated in seven cases. Preceding history of viral hepatitis was elicited in two cases. All the patients did not have lymphadenopathy and hepatosplenomegaly. Figure2 a,b.

CHRONIC INFLAMMATION consisted 6 cases of Males and 4 cases of females . Age range is 18-46. The average time from onset of symptoms to diagnosis was three months. All patients presented with on and off fever, two patients had multiple cervical lymphadenopathy. FNAC of cervical lymphnodes showed chronic granulomatous lymphadenitis in four cases.

SUBLEUKEMIC LEUKEMIA was observed in 5 male cases and 3 female cases. Age range was 2.5 – 5 years. The average time from onset of symptoms to diagnosis was 15 days. 2 children presented with pallor, 2 children with pallor and purpuric spots and 2 children with pneumonia. Figure3a showing lymphoblasts in bone marrow cell trail.

IN NON HODGKINS LYMPHOMA out of 4 cases 2 cases were males and 2 cases were females. The average time from onset of symptoms to diagnosis was 6 months. Both patients presented with generalized lymphadenopathy. Both have hepato splenomegaly. Figure3(b,c) trephine biopsy of bone marrow in non hodgkins lymphoma.

MULTIPLE MYELOMA diagnosed in 4 cases of females. All cases are 50 and above 50 years. One patient was presented with generalized bony pains and swelling in the left parietal region in the scalp. X-ray skull of the patient showed punched out lesions. Another patient presented with fracture neck of right femur. All patients’ urine was positive for Bence Jones proteins, peripheral smear shows RBC rouleaux formation and plasma cells in the bone marrow Figure3( d).

The variation in the frequency of various diagnostic entities causing pancytopenia has been attributed to difference in methodology and stringency of diagnostic criteria, geographic area, period of observation, genetic differences, varying exposure to myelotoxic agents.

This study showed that pancytopenia can be the presenting feature of many diseases, with megaloblastic anaemia, hyersplenism and aplastic anaemia constituting the largest sub groups in the cases studied. Hematological values in these major groups showed considerable overlap making bone marrow examination mandatory to reach a diagnosis. Though neutropenia is the most marked aspect of pancytopenia, it was the first presenting feature in the present study.

The most important test is bone marrow examination, either in confirming the diagnosis or in excluding a primary marrow involvement and suggesting alternative investigations. Bone marrow aspiration is not helpful in those with aplastic anaemia or marrow infiltrations even if fragments were aspirated. In such case bone marrow biopsy is helpful. Bone marrow aspirate specimens are superior for morphological detail over biopsy, while biopsy specimens provide a more reliable index of cellularity and often reveal marrow infiltration, fibrosis and granulomas which are not detected on aspiration. Thus both the procedures are complimentary in diagnosis in the setting of pancytopenia. If hypersplenism and megaloblastic anaemia are detected clinically or on peripheral smear, an aspirate alone is enough for the diagnosis.

The incidence of megaloblastic anaemia varies from 0.8% to 32.26% of all pancytopenia patients (21). Tilak, V. and Jain, R.(3) studied 77 cases of pancytopenia and observed that megaloblastic anaemia and aplastic anaemia were the major causes of pancytopenia. They suggested that bone marrow examination would be differed in those cases presenting with hepatosplenomegaly and hyper segmented neutrophils in the peripheral smear. These patients could be put on hematinc with close hematological follow-up.

In our study also in the cases of pancytopenia, where the patients were not willing for bone marrow aspiration, peripheral smear showing macrovalocytes, a therapeutic trail of parenteral vit.B12 injection and folic acid was given and
after an interval of 5 days, the counts were observed to have improved indicating the deficiency of these factors for the pancytopenia.

Megaloblastic anaemia is the most frequent cause of pancytopenia constituting 26.41% of all cases. R. Kumar et al (4) from AFMC and AHRR, NEW DELHI found that megaloblastic anaemia causing pancytopenia in 22.29% of cases in 166 pancytopenic patients. Our finding is in accordance with that of Tilak. V et al (3) who also found megaloblastic anaemia as the commonest cause of pancytopenia. Similar results have been reported from other Indian centers. Sen., et al. from Rohtak (22) also found megaloblastic anaemia to be the commonest cause (39%) in a study of 191 pancytopenic patients. Kale, P. et al (23) from Mumbai in a study of 65 pancytopenic patients detected megaloblastic anaemia in 25.4% cases. Incidence of pancytopenia due to megaloblastic anaemia reported by different authors from different parts of the India is shown in table-2. The commonest cause of pancytopenia, reported from various studies throughout the world has been aplastic anaemia. This seems to reflect the higher prevalence of nutritional anaemias in Indian subjects.

Hypersplenism is the second most frequent cause of pancytopenia in our study. Cause of pancytopenia in our study constituting 24.53%. Similar incidences have been reported by Bhawana et al (24) from Pondicherry who reported 54 cases of hypersplenism among 207 cases of pancytopenia constituting 28%. R.S.Bindu et al (14) found that in 5.26% of cases of pancytopenia, hypersplenism is the cause. R.Kumar et al (4) found hypersplenism to be the cause of pancytopenia in 11.45% of cases. Hypersplenism in our area is due to portal hypertension and chronic malarial infection. Pancytopenia occurring in patient with falciparum malaria was also partly due to the reason that marrow is megaloblastic. As treatment of megaloblastic anaemia is easy this disorder should always be considered in the evaluation of pancytopenia.

Hypocellular marrow is the cause of pancytopenia in 13.20% of cases of our study, aplastic anaemia is the commonest cause of pancytopenia in the studies of Pradhan SP et al from Berhampur(25), Kumar R. et al from AFMC and AHRR New Delhi(4) & Bindu RS. et al from Aurangabad(14) constituting 26%, 29.52% and 36.84% respectively. Tilak.V. et al from PGIMER Chandigarh(3) reported aplastic anaemia to be the cause of pancytopenia in 7.79% of the cases.

Singh.T et al 1999(26) suggested that lack of required higher number of plasma cells in a bone marrow aspirate in cases of early myeloma could be because of the focal nature of disease process at that time. In such cases, a marrow biopsy is indicated for early recognition. We also observed 21% of plasma cells in one of our cases of early myeloma who presented with pancytopeny but biopsy could not be done.

In our study tuberculosis is diagnosed in two cases even though chronic inflammation is suggested in eight cases. Tuberculosis is rare but important cause of pancytopenia.

Tuberculosis should be considered as differential diagnosis, if fever or hepatospleonomegaly are associated (27). The diagnosis may be difficult as pulmonary involvement is usually not a feature but confirmation is often possible by liver biopsy(28). Non hodgkins lymphoma and micro normoblastic erythroid hyperplasia(un explained cause) are other causes of pancytopeny encountered in our study.

6. Conclusion

Out of 1050 patients who were admitted in Rajiv Gandhi Institute of Medical Sciences, KADAPA , A.P., INDIA 106 patients have pancytopenia. Of these patients, the major group (28) is of megaloblastic anaemia which constituted 26.41%. The second major group is formed by hypersplenism which constituted 26 cases forming total of 24.53%, the third group is formed by aplastic anaemia which constituted 14 cases forming a total of 13.20%. Cases of chronic inflammation constituted 8 cases forming 7.55% of these two cases are of tuberculosis forming 1.89% cases. Subleukemic leukemia constituted 8 cases forming 7.55%. Non hodgkins lymphoma and multiple myeloma constituted 4 cases each forming 3.77%. In cases of unexplained pancytopeny especially in children, a therapeutic trial of parenteral Cyanocobalamin & Folic acid may be tried because of the prevalence and occurrence of the same cause as observed in the present study.

7. Future Scope

If pancytopenia is diagnosed on peripheral smear examination in correlation with blood counts identification of cause of pancytopenia is essential for management of the case. The diagnosis of megaloblastic anaemia is possible by blood picture, red cell indices, bone marrow aspiration findings and biochemical tests. To diagnose aplastic anaemia bone marrow biopsy is mandatory and to know the specific cause clinical examination, history including treatment with drugs like antimetabolites, exposure to toxic chemicals, infections, and other viral diseases are required. So study of pancytopenia is important and necessary and lot of research is needed to follow better treatment approaches and to give better quality of life to patients.

References

[7] Current Medical Diagnosis and Treatment, 2002

**Figure-1. Megaloblastic anaemia**

a) peripheral smear showing macroovalocytes and hyper segmented neutrophils.

b) giant metamyelocyte in a case of megaloblastic anaemia in bone marrow

c) megaloblasts with sieve like chromatin and sea blue cytoplasm in bone marrow

D) hyper celluloarmarrow in a case of megaloblastic anaemia

**Figure-2.**

a) severe reduction of haematopoietic cells and increased fat spaces in bone marrow in aplastic anaemia (leishman 50x)

b) trephine biopsy showing hypo cellular marrow and increased fat spaces in aplastic anaemia 50x H&E

c) erythroid hyperplasia of bone marrow in hypersplenism (leishman 1000x)

d) QBC for malaria parasite positive
Table 1: Causes of Pancytopenia in 106 Patients

<table>
<thead>
<tr>
<th>S.No</th>
<th>Causes Of Pancytopenia</th>
<th>No. Of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MEGALOBLASTIC ANAEMIA</td>
<td>28</td>
<td>26.42%</td>
</tr>
<tr>
<td>2</td>
<td>APLASTIC ANAEMIA</td>
<td>14</td>
<td>13.20%</td>
</tr>
<tr>
<td>3</td>
<td>HYPERPSEPLENISM</td>
<td>26</td>
<td>24.53%</td>
</tr>
<tr>
<td>4</td>
<td>DIMORPHIC ANAEMIA</td>
<td>8</td>
<td>7.55%</td>
</tr>
<tr>
<td>5</td>
<td>CHRONIC INFLAMMATION</td>
<td>8</td>
<td>7.55%</td>
</tr>
<tr>
<td>6</td>
<td>SUBLEUKEMIC LEUKEMIA</td>
<td>8</td>
<td>7.55%</td>
</tr>
<tr>
<td>7</td>
<td>MICRONORMOBLASTIC ERYTHROID HYPERPLASIA (UNEXPLAINED CAUSE)</td>
<td>4</td>
<td>3.77%</td>
</tr>
<tr>
<td>8</td>
<td>NON HODGKINS LYMPHOMA</td>
<td>4</td>
<td>3.77%</td>
</tr>
<tr>
<td>9</td>
<td>MULTIPLE MYELOMA</td>
<td>4</td>
<td>3.77%</td>
</tr>
<tr>
<td>10</td>
<td>TUBERCULOSIS</td>
<td>2</td>
<td>1.89%</td>
</tr>
<tr>
<td></td>
<td>TOTAL</td>
<td>106</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 2: Commonest Cause of Pancytopenia in Different Places of India

<table>
<thead>
<tr>
<th>S.No</th>
<th>Study</th>
<th>Country</th>
<th>Year</th>
<th>No of Cases</th>
<th>Commonest Cause of Pancytopenia</th>
<th>Percent</th>
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<tr>
<td>2</td>
<td>Sen., et al</td>
<td>Rohtak</td>
<td>1996</td>
<td>191</td>
<td>Megaloblastic anaemia</td>
<td>39.00%</td>
</tr>
<tr>
<td>3</td>
<td>Tilak.V et al</td>
<td>Chandigarh</td>
<td>1999</td>
<td>77</td>
<td>Megaloblastic anaemia</td>
<td>68.83%</td>
</tr>
<tr>
<td>4</td>
<td>Bhavana et al</td>
<td>Pondicherry</td>
<td>1999</td>
<td>207</td>
<td>hypersplenism</td>
<td>28.00%</td>
</tr>
<tr>
<td>5</td>
<td>Bindu R.S et al</td>
<td>Aurangabad</td>
<td>2000</td>
<td>38</td>
<td>Aplastic anaemia</td>
<td>36.84%</td>
</tr>
<tr>
<td>6</td>
<td>Kumar et al</td>
<td>New delhi</td>
<td>2001</td>
<td>166</td>
<td>Aplastic anaemia</td>
<td>29.52%</td>
</tr>
<tr>
<td>7</td>
<td>Khunger JM et al</td>
<td>New delhi</td>
<td>2002</td>
<td>200</td>
<td>Megaloblastic anaemia</td>
<td>22.29%</td>
</tr>
<tr>
<td>8</td>
<td>PRESENT STUDY</td>
<td>KADAPA,A.P.</td>
<td>2014</td>
<td>106</td>
<td>Megaloblastic anaemia</td>
<td>26.41%</td>
</tr>
</tbody>
</table>

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