

Clinical analysis of 43 cases of chronic benzene poisoning

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Abstract

Benzene can result in bone marrow suppression. Chronic benzene poisoning (CBP) can be found among workers with excessive benzene exposure. CBP could give the appearance of different types of disorders such as leukopenia, agranulocytosis, anemia, pancytopenia, aplastic anemia (AA), myelodysplastic syndrome (MDS), and leukemia. This paper describes 43 CBP cases with the patients' ages ranging from 18 to 36 years (average: 23 years). Among them, 13 (30%) were male and 30 (70%) were female. Their job titles were furniture maker, shoemaker, industrial painter and metal shop worker. Their work durations ranged from 1.5 to 72 months (average: 14 months). Benzene levels in these workplaces exceeded 30 mg/m^3 . Ten of the 43 cases (23%) were diagnosed as mild cases of CBP, another 10 (23%) were moderate, and 23 (53%) were severe. Treatment for CBP included the following: cessation of benzene exposure, general supportive therapy, antibiotics, vitamins, corticosteroids, androgens, colony-stimulating factors (G-CSF, GM-CSF), blood component therapy, and traditional Chinese medicine. Thirty-three (77%) of the cases recovered completely, nine (21%) cases improved, and one (2%) died. In general, prognosis of CBP cases is optimistic when appropriate treatment is given. However, a few of the benzene-induced AA cases showed no response to treatment, which raises questions about the traditional view of the pathogenesis of the illness. Furthermore, only a part of the population with the same level of benzene exposure would suffer from the disease. Still, CBP cases with the same benzene exposure level exhibited different extents of severity of the illness. This evidence suggests strongly the existence of individual susceptibility. Detection of the biological markers regarding the individual susceptibility would be valuable for screening workers who are not suitable to be exposed to benzene.

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1. Introduction

Benzene is one of the aromatic hydrocarbons, a colorless organic solvent derived from petroleum refining. Pure benzene is no longer widely employed in indus-

tries, but benzene-containing solvents, such as the extraction agent of vegetable oil and animal fat, and the solvents or thinners for rubber, resins, paints, and glues could be found as an industry production material. Occasionally, benzene-containing solvents are even used as a degreaser for metal work-pieces.

Benzene can be absorbed through the respiratory tract or via epidermal contact. Neglect of ventilation in the work place and/or failure to use personal protective

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equipment when using benzene-containing solvents will increase the incidence of benzene poisoning.

It is well known that benzene is a bone marrow toxin, which can cause bone marrow suppression [1,2]. Clinical pictures of the chronic benzene poisoning may vary significantly, from leukopenia, thrombocytopenia, pancytopenia, and aplastic anemia (AA) to leukemia [3,4].

Diagnosis and treatment of 43 cases of chronic benzene poisoning (CBP) at Guangdong Poison Control Center (GDPCC) were analyzed for this paper.

2. General data of the cases

All 43 cases were inpatients at our center and were collected from four kinds of factories during the past 4–5 years. Among them, 13 were male (30%) and 30 were female (70%). The age ranged from 18 to 36 years, with the average age being 23.1 years. Twenty-nine (67.4%) cases were furniture makers, 12 (27.9%) were shoemakers, 1 (2.3%) was an industrial painter and the last one (2.3%) was a punch worker. Their work durations ranged from 1.5 to 72 months; the average was 14.3 months. The furniture makers used sprayers to spray the benzene-containing glue on the artificial sponge and assemble them into the final shape during working. The shoemakers used brushes to smear the benzene-containing glue on the bottoms of shoes during the production procedure. The industrial painter used benzene-containing paint and thinner to paint small parts; and the punch worker used a benzene-containing degreasing agent to clean the work-pieces. Benzene vaporized during the working procedure, and ventilation in the workplaces was insufficient. Ambient benzene levels in the workplaces generally exceeded 30 mg/m^3 , and the peak level was 92.2 mg/m^3 . In the workplaces, there were other chemicals including toluene, xylene, ethyl acetate, butyl acetate, and ethylbenzene. The route of benzene exposure was mainly through the respiratory tract, and secondarily through dermal contact. Only a fraction of the employees working in the same workplaces showed hematological abnormalities, and the rest were normal.

3. Diagnosis and differential diagnosis

All the 43 CBP cases were inpatients. Their medical examinations included confirmation of the history

of benzene exposure, routine physical check-ups, peripheral blood routine examinations at least three times, and if necessary bone marrow smears and biopsies during hospitalization. They were diagnosed according to the diagnostic standard for CBP as follows:

(1) Mild cases of CBP:

Those who suffered from leukopenia (the white blood cell (WBC) count ranged from 3.0×10^9 to $4.0 \times 10^9/\text{L}$, or the neutrophilic granulocyte count was less than $2.0 \times 10^9/\text{L}$).

(2) Moderate cases of CBP:

(a) Those cases whose WBC counts were less than $3.0 \times 10^9/\text{L}$, or the neutrophilic granulocyte count was less than $1.5 \times 10^9/\text{L}$.

(b) Leukopenia plus anemia.

(c) Leukopenia plus thrombocytopenia.

(3) Severe cases of CBP:

(a) *Pancytopenia*: Those cases who had low red blood cell (RBC), WBC, hemoglobin (Hgb), and platelet counts, but bone marrow smear and biopsy examinations were not hypocellular.

(b) AA.

(c) Myelodysplastic syndrome (MDS).

(d) Leukemia.

The patients were determined to be free of the diseases that may cause similar symptoms and signs, such as leukopenia or AA due to other causes, subleukemic leukemia, and paroxysmal nocturnal hemoglobinuria (PNH). As a result, 10 cases (23%) were diagnosed as mild, another 10 (23%) as moderate, and 23 (53%) as severe CPB cases. Among the severe cases, 13 had pancytopenia and 10 had aplastic anemia. None of the study's patients was found to have MDS or leukemia during the hospitalization and a 3-month follow-up after discharge.

Tables 1–3 show the peripheral blood cell count results of the 43 cases when admitted.

4. Therapy

The therapy varied for different groups, but included:

(1) Workers would be removed from benzene exposure and sent or transported from other hospitals

Table 1
Blood cell counts of the 10 mild cases

Blood cells	Median	Range
RBC ($\times 10^{12}/L$)	3.70	3.51–4.34
Hgb (g/L)	116	106–136
WBC ($\times 10^9/L$)	3.45	3.0–3.7
Lymphocytes ($\times 10^9/L$)	1.1	0.9–1.5
Platelets ($\times 10^9/L$)	115	75–186
MCV (fl)	82	78–102
MCHC (g/L)	384	323–396

Table 2
Blood cell counts of the 10 moderate cases

Blood cells	Median	Range
RBC ($\times 10^{12}/L$)	3.66	2.5–4.95
Hgb (g/L)	110.5	68–140
WBC ($\times 10^9/L$)	2.35	0.7–3.7
Lymphocytes ($\times 10^9/L$)	0.8	0.3–1.2
Platelets ($\times 10^9/L$)	78.5	21–172
MCV (fl)	79.5	67–98
MCHC (g/L)	356	310–393

to GDPCC for hospitalization as soon as the patients were suspected of suffering from CBP.

- (2) The mild cases were given general supportive therapy, which including proper nutrition, vitamins, agents stimulating granulocytopoiesis such as Batilol (a shark liver extract) and Leucogen (a derivative of cysteine), and traditional Chinese medicine.
- (3) Besides general supportive therapy, the moderate cases were treated with injections of recombinant human granulocyte colony-stimulating factor (G-CSF) or recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF)

Table 3
Blood cell counts of the 23 severe cases

Blood cells	Median	Range
RBC ($\times 10^{12}/L$)	2.41	0.81–3.03
Hgb (g/L)	72.5	28–106
WBC ($\times 10^9/L$)	1.45	0.2–3
Lymphocytes ($\times 10^9/L$)	0.65	0.1–1.5
Platelets ($\times 10^9/L$)	23.5	11–78
MCV (fl)	86	78–105
MCHC (g/L)	382	328–408

if their WBC counts were lower than $2.0 \times 10^9/L$, or the neutrophilic granulocyte count was less than $1.0 \times 10^9/L$. Blood component therapy with RBC or platelet transfusions would be applied occasionally if the patient experienced low hemoglobinemia (Hgb < 60 g/L) or significant hemorrhage.

- (4) Treatment of severe CBP cases, the case of pancytopenia and AA, was difficult and complicated, and often lasted for a long period of time. Complications such as intracranial hemorrhage and septicemia could be lethal. Besides general supportive therapy, G-CSF, GM-CSF, corticosteroids, androgens, repeat RBC and platelet transfusions, and antibiotics were often applied. Intensive care would often be necessary for extremely severe cases.

5. Outcome

Among the 43 cases, 33 cases (77%) including 10 mild cases, 10 moderate cases and 13 severe cases recovered completely. Their clinical symptoms and signs subsided, the peripheral blood examination results returned to normal at least three times during hospitalization, and the bone marrow examination results become normal before discharge. Their condition remained stable during a 3-month period of follow-up. Nine cases (21%) that were diagnosed as pancytopenia or AA improved significantly. Their results of peripheral blood routine examination and bone marrow examinations were near normal at time of discharge, and their conditions were satisfactory even during the 3–4-month follow-up. One AA case (2%) showed poor effect to the therapy and died of septicemia and severe intracranial hemorrhage.

Table 4 shows the time to recovery or significant improvement according to the recovery or near recovery of the peripheral blood cell counts. The one death was not included in the severe group.

Table 4
Time (days) for recovery or significant improvement

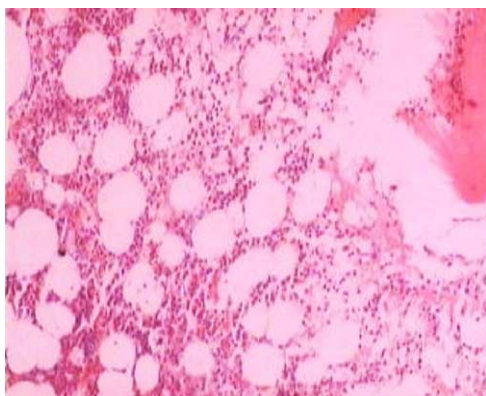
Group	Median	Range
Mild	106	11–530
Moderate	171	14–512
Severe	159	16–1445

6. Typical cases

6.1. Case 1

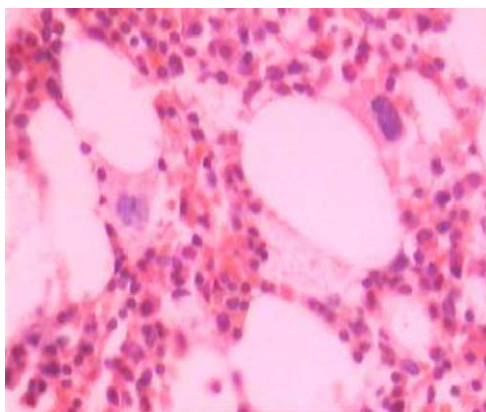
Age: 24 years; female; admission number: 6922; admission date: October 25, 1999; a furniture maker; work duration: 20 months. In a furniture factory, her job was to spray the glue on the surface of the artificial sponge pieces by a sprayer and assemble them into the final shape. The glue contained benzene, and the air benzene level was well over 30 mg/m^3 . The exposure was mainly from respiratory inhalation, and partly through skin contact. After 12 months of working, she felt dizziness. Ecchymoses were found on her lower limbs 1 month before admission. She was suspected to suffer from leukopenia and ane-

mia due to benzene exposure during a regular physical check-up in her factory. Then, she was sent to GDPCC. Upon admission, ecchymoses were seen on her lower limbs, and her peripheral blood routine examination showed: WBC $2.6 \times 10^9/\text{L}$, neutrophilic granulocytes $1.1 \times 10^9/\text{L}$, RBC $3.50 \times 10^{12}/\text{L}$, Hgb 87 g/L , and platelets $102 \times 10^9/\text{L}$. The WBC count and hemoglobin was significantly low, while the RBC and platelet counts were normal. Both the bone marrow smear and biopsy examination results were normal (Slides 1 and 2). She was diagnosed as having a moderate degree of CBP (leukopenia plus anemia). During hospitalization, she was treated with sodium inosine monophosphate, Vitamin B₄, Batilol, Leucogen and traditional Chinese medicine. Her WBC counts increased gradually and returned to normal within 2



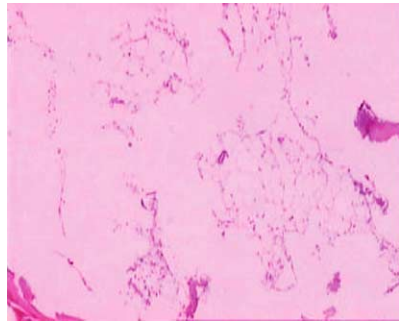
10 × ;
H&E;
Paraffin;
Showing normal
bone marrow.

Slide 1. Case 1.



40 × ;
H&E;
Paraffin;
Showing normal
bone marrow.
2 megakaryocytes
are shown.

Slide 2. Case 1.



4 × ;
H&E;
Paraffin;
Hypocellular bone marrow; fat
cells occupied 80% of the bone
marrow cavity.

Slide 3. Case 2, before treatment.

months. The peripheral blood routine examination result at discharge was: WBC $5.1 \times 10^9/L$, neutrophilic granulocytes $3.5 \times 10^9/L$, granulocytes 59%, RBC $3.98 \times 10^{12}/L$, Hgb 118 g/L, and platelets $120 \times 10^9/L$. Peripheral blood counts remained stable for a 3-month follow-up after discharge. It is indicated that she had totally recovered.

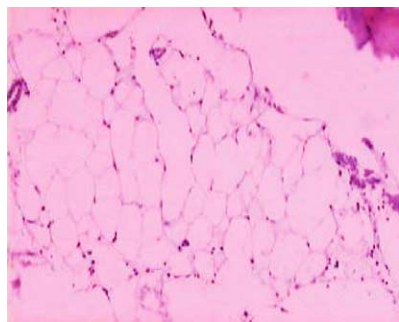
6.2. Case 2

Age: 23 years; female; admission number: 7701; admission date: April 10, 2001; worker from an electronics factory; work duration: 11 months. In the factory, her job was to degrease the manufactured pieces from a punch by using a detergent with a benzene-containing solvent. Benzene exposure occurred both by inhalation and by dermal contact. The air benzene level in her workplace ranged from 30 to 92.2 mg/m³. After working in the factory for 6 months, the patient complained of dizziness, and began to have an excessive menorrhea for 4 months before admission. She was suspected to

suffer from aplastic anemia in a local hospital and then transported to GDPCC.

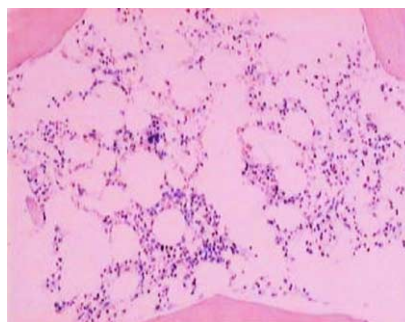
When admitted, the patient looked pale and had a low fever (37.5 °C); the pulse was 125/min. She also had bleeding gums and ecchymoses were seen on her extremities. Results of routine urinary test, Ham's test, sugar water test, urine occult blood test, Rous test, Coombs' test and renal function test were negative. Results of the peripheral blood routine examination was as follows: RBC $1.97 \times 10^{12}/L$, Hgb 65 g/L, WBC $2.8 \times 10^9/L$, neutrophilic granulocytes $1.0 \times 10^9/L$, and platelets $22 \times 10^9/L$. All counts were significantly lower than normal. Bone marrow smear and biopsy examination results showed "hypocellular bone marrow; fat cells occupied 80% of the bone marrow cavity and no megakaryocytes could be seen", which strongly indicated the diagnosis of benzene-induced AA (Slides 3 and 4). She then was diagnosed as a benzene-induced AA case.

During hospitalization, besides the common treatment procedures such as general support therapy,



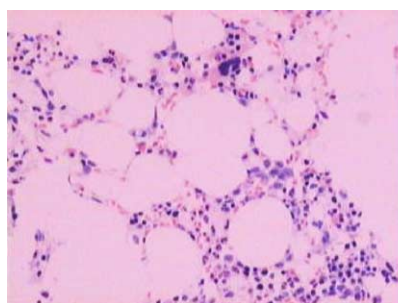
20 × ;
H&E;
Paraffin;
Hypocellular bone marrow; fat
cells occupied 80% of the bone
marrow cavity. No
megakaryocytes could be seen

Slide 4. Case 2, before treatment.



10 × ;
H&E;
Paraffin;
Improved bone marrow. Fat
cells occupied about 50% of the
cavity. A megakaryocyte could
be seen in the field.

Slide 5. Case 2, after treatment.



20 × ;
H&E;
Paraffin;
Improved cellular bone marrow.
Fat cells occupied about 50% of
the cavity. A megakaryocyte
could be seen.

Slide 6. Case 2, after treatment.

she was also given G-CSF, GM-CSF, frequent blood component therapy, corticosteroids, androgens, human globulin and traditional Chinese medicine. After 8 months of hospitalization, her condition seemed to have worsened. Hemorrhage became more general, and she developed an infection; her temperature reached 39.5 °C. After being given antibiotics, human serum globulin, transfusion of RBC and platelets, the episode subsided.

The patient was nearly completely recovered after 2.5 years of hospitalization. Her peripheral blood routine examination results were improved considerably except for the neutrophilic granulocyte count (RBC $3.72 \times 10^{12}/L$, Hgb 121 g/L, WBC $4.0 \times 10^9/L$, neutrophilic granulocytes $1.3 \times 10^9/L$, platelets $67 \times 10^9/L$). Bone marrow smear and biopsy results were: “nearly normal bone marrow; fat cells occupied about 50% of the cavity, and one to two megakaryocytes can be seen” (Slides 5 and 6). The patient was discharged on April 4, 2004, and her peripheral blood routine examination results remained stable during the 4 months of follow-up.

7. Discussion

The outcome of the 43 cases suggests that short-term prognosis of mild and moderate CBP could be optimistic. Even the prognosis of severe CBP such as the benzene-induced AA would be better than that of idiopathic aplastic anemia if proper treatments were provided. However, the long-term prognosis of the 43 cases still remains unknown because longer follow-up is required. Only the results of a long-term follow-up study can provide a definite conclusion to this question due to the long incubation time of certain benzene-induced neoplasms of blood-forming tissues.

Some other questions regarding CBP remain unknown. Firstly, our 43 cases of CBP came from different kinds of factories. About 75–85% of their colleagues in the same settings showed no change on peripheral blood routine examination. This indicates the possibility that different individual susceptibilities to benzene exist [5].

Although the use of pure benzene has been banned and other solvents have been substituted for benzene

for years, benzene is still being used in fact. Most of the organic solvents are obtained from petrol which contains benzene. Organic solvents are being used in many factories, such as toluene, xylene, gasoline and thinners which always contain a certain amount of benzene. It would be quite difficult to produce benzene free organic solvents for industrial use, and benzene exposure would exist in some kinds of production procedure for a period of time. Therefore, if specific biomarkers related to individual susceptibility to benzene could be identified and applied clinically, they could be valuable to screen out those workers who should not be involved in jobs with benzene exposure.

The ideal way to prevent benzene poisoning would be to lower the occupational benzene limits and finally prohibit the use of benzene. To allow the workers not susceptible to benzene to engage in benzene-related jobs would certainly not be right. However, before the use of benzene is totally banned, a screening method might be one of the realistic and temporary solutions.

Therapy for benzene-induced AA mainly includes general supportive therapy, corticosteroids, androgens, G-CSF and GM-CSF at present [6]. Twelve of the 43 CBP cases were benzene-induced AA cases. They received the same therapy. While most of the patients responded favorably to the treatment, these treatments were not so effective in a few of the others who were not so severe as those cases above during the early stage of the illness. It has been reported that the traditional immunosuppressive therapy might not be effective in some of the benzene-induced aplastic anemia cases [6]. It seems that there might be more than one type of benzene-induced AA, and new viewpoints are emerging regarding pathogenesis of the illness. The potential biomarkers for the identification of the different types of the illness will provide new approaches for more effective therapies for the disease.

Transplantation of bone marrow or stem cells has undergone rapid progress during recent years. However, due to the optimistic prognosis of most of the benzene-induced AA cases, and the serious complications of transplantation of bone marrow or stem cells, it is always difficult for doctors when making a decision whether the transplantation therapy should be undertaken or not on a benzene-induced AA case. Perhaps this is why this new therapy is not so commonly used for the treatment for benzene-induced AA. Recently, an attempt at a new therapy, the cell-based immunotherapeutic approach, was applied for a group of the benzene-induced cases that had failed immunosuppressive therapy. It is reported that the preliminary results seem to be optimistic [7].

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