IDIOPATHIC THROMBOCYTOPENIC PURPURA IN ELDERLY PATIENT: 2 CASE REPORTS AND LITERATURE REVIEW

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Summary
Bleeding is not an uncommon reason of hospital admission in elderly people. We report 2 elderly patients with diagnosis of Idiopathic Thrombocytopenic Purpura (ITP). Oral steroid was started with satisfactory platelet counts response in both patients. One developed steroid myopathy and another became immuno-compromised resulting in severe chest infection and death. The clinical, patho-physiological features and treatment modalities for ITP in elderly patients were reviewed. One should be aware that ITP does occur among elderly and treatment complications should be watched out for.

Introduction
Adult Chronic Idiopathic Thrombocytopenic Purpura (ITP) is a common haematological disorder. It is estimated that about 14,000 to 16,000 new cases occur each year in the United States. The incidence is about 1 in 10,000 in the general population. It occurs most commonly during the third and fourth decade of life, with a female to male ratio from 2:1 to 3:1. Although it is generally considered to be a disease of the paediatric and young adult age group, it does occur in the elderly and is sometimes life-threatening. The oldest reported patient with ITP was 89. We report two elderly patients with ITP and review literature on its management.

Case 1
Ms. L.C. was a 80 years old lady. She had a history of hypertension and diabetes mellitus that were well controlled with nifedipine and metformin. She presented in July 1998 with spontaneous bruising for a few days. Platelet count on admission was 4 x 10^9/L. There was no history of herbs or other drugs intake. Physical examination was unremarkable except some bruises over limbs. Blood film was normal and bone marrow examination confirmed megakaryocytopenesis consistent with peripheral consumption or destruction of platelets. The anti-nuclear factor was negative. Oral prednisolone was started at a dose of 40mg daily (1mg/kg/day) and satisfactory response was obtained within a few days. She was discharged about 10 days later with platelet count 150 x 10^9/L. She developed proximal muscle weakness after 3 weeks of full dose steroid. Muscle enzymes were normal on admission and the blood sugar was in fair control. The weakness was thought to be due to steroid myopathy, which improved after the steroid dose was tapered down to 20mg daily. The platelet count maintained at around 100-170 x 10^9/L on subsequent follow up.

Case 2
Ms C.K. was a 79-year-old lady with good past health. She presented to the accident and emergency department in November 1998 with intermittent gum bleeding and petechiae for a few weeks. There was no history of recent viral illness nor drug consumption. Spleen and lymph nodes were not palpable. The platelet count on admission was 13 x 10^9/L. Blood picture showed hypochromic microcyctic anaemia. Bone marrow revealed i) increased number of megakaryocytes, consistent with peripheral consumption, and ii) absent iron stores, consistent with iron deficiency anaemia. Upper endoscopy performed was normal. USG of the abdomen showed a normal sized spleen. Further blood tests showed a positive anti-nuclear factor but the anti-double stranded DNA, anti-ENA and ANCA antibodies were all negative. A diagnosis of ITP was made and oral prednisolone 60mg daily (1mg/kg/day) was started. The platelet level responded...
satisfactorily for the first 2-3 weeks but dropped significantly when the dose was tapered. Danazol 200mg twice daily was added after the patient had turned down the suggestion of splenectomy. The platelet count was then around 70-150 x 10^9/L.

She was readmitted three months later because of pneumonia and respiratory failure. At that time the dosage of prednisolone was at 20mg daily. Sputum culture grew Pseudomonas aeruginosa. Despite antibiotics, her condition deteriorated rapidly and she developed sepsis syndrome with multi-organs failure. She finally succumbed after one week of intensive support.

Pathophysiology

Chronic ITP is presumably be caused by anti-platelet autoantibodies. The autoantibodies bind to autologous platelets which are then rapidly cleared from the circulation by the mononuclear phagocyte system via macrophage Fc receptors. This results in a significant reduction in the platelet life span, from 7 - 10 days normally, to a few hours only. Most patients have IgG anti-platelet autoantibodies and most autoantibodies (85%) are directed against target antigens on the glycoprotein (GP) IIb-IIIa, although some are specific for GP Ib-IX or GP Ia-IIa. Although most antibodies function as opsonins and accelerate platelet clearance by phagocytic cells, occasionally antibodies impair platelet function. Demonstration of platelet antibodies is not routinely recommended in establishing the diagnosis, as their specificity is doubtful. Its titre neither correlates with severity of thrombocytopenia nor appears to be a useful prognostic test.

Diagnosis

The diagnosis of ITP is by exclusion. In elderly patients, the differential diagnosis of myelodysplasia and drug induced thrombocytopenia should be carefully evaluated. The presence of Pelger-Huet anomaly, nucleated red blood cells, and immature granulocytes in peripheral blood smear should alert one to suspect myelodysplasia. Bone marrow examination is considered appropriate to establish the diagnosis in patients over 60. Besides myelodysplastic syndrome, drug-induced thrombocytopenia has to be ruled out. Common offending drugs include quinine bisulphate, heparin, sulphonamides, sulphonylureas, dipyridamole, rifampin and hydrochlorothiazide. All these are not uncommonly prescribed for elderly patients and have to be watched out for. Other autoimmune diseases and lymphoproliferative disorder also need to be excluded.

Clinical presentation

Clinical bleeding occurs when the degree of thrombocytopenia varies between 10-30 x 10^9/L. Most patients come to medical attention because of petechiae or purpura over a course of several days. On some occasions, evidence of cutaneous bleeding may be accompanied by bleeding from other mucosal sites, presenting as epistaxis, gum bleeding, menorrhagia or less commonly, melaena. Rarely, patients may present with intracranial haemorrhage. If left untreated, about 5% of adults with chronic ITP died of haemorrhagic complications. Severe bleeding episodes are more common in patients age >60 or in those with history of bleeding.

Guthrie et al reported a 52.5% incidence of life-threatening or fatal bleeding in their series of older adult patients. Stasi et al also reported that bleeding episodes of the central nervous system tend to occur more frequently in the elderly.

Treatment

The ITP Practice Guideline was published in 1996 by the American Society of Haematology. However, most of the reviewed literature on the treatment of ITP were based on case studies of selected patients whose course cannot be evaluated in the absence of a control group. Hopefully, the guideline would soon be updated with evidence-based recommendations.

The principal therapeutic options for elderly patients are similar to that for young adults. They include corticosteroid, intravenous immunoglobulin and splenectomy. Danazol and immunosuppressive agents are used in cases refractory to usual treatment. However, there is yet no direct evidence demonstrating that any of these treatments reduce bleeding complications or mortality from ITP. Elderly patients with platelet counts that exceed 50 x 10^9/L do not routinely require treatment. Treatment is indicated in patients with platelet counts < 30 x 10^9/L and in patients who have counts < 50 x 10^9/L plus mucus membrane bleeding (or risk factor for bleeding, such as hypertension, peptic ulcer or potential for trauma).

1) Steroids

Glucocorticoid has been the standard initial treatment since the 50’s. It prevents the sequestration of antibody-coated platelets by the spleen. The inhibition of phagocytosis is associated with decreased Fc γ-receptor expression on macrophages. Since platelet-associated IgG is also decreased, it is likely that corticosteroid impair antibody production and/or binding to platelets.
Although it has been suggested that very high doses of glucocorticoid (e.g. intravenous methylprednisolone) may result in a more rapid increase of the platelet count\textsuperscript{16,17}, one study suggested equal efficacy among different dose regimens\textsuperscript{18}. Cardiac arrhythmia (e.g. atrial fibrillation) has also been reported during the administration of pulse steroid.\textsuperscript{19} It was thus recommended that intravenous methylprednisolone should be used only in life-threatening situations\textsuperscript{2}. Continuous ECG monitoring should be adopted during the treatment.

Although the platelet count may rise as early as on the third day after treatment, the response can be delayed beyond the first week. Good (>100 x 10\textsuperscript{9}/L) and satisfactory (>50 x 10\textsuperscript{9}/L) response occurs in 65-85\% of patients but sustained responses after discontinuation of the drug occurs in only less than 25\% of patients\textsuperscript{2,20}. There seems to have no major differences between old and young patients in the response to steroids\textsuperscript{12}. Irrespective of age, it is generally recommended that prednisolone at dose of 1mg/kg/day is started at diagnosis. If the platelet count normalizes, the dose should be continued for one to two weeks and then tapered by 10mg per week until the dose reaches 0.5mg/kg of body weight and by 5mg per week thereafter\textsuperscript{1}. The purpose of long term corticosteroid is to maintain the platelet count at a safe level (e.g. >30 x 10\textsuperscript{9}/L). It is not necessary to raise the platelet count to normal for that would often require prohibitive doses of corticosteroid. The risk of serious side effects is high. Our first patient was put on prednisolone 40mg daily after the diagnosis has been made. The full dose steroid has been maintained for three weeks before it was reduced. The second patient was put on prednisolone 60mg daily at the beginning but the dose failed to be tapered. After danazol was added, the steroid could be slowly reduced to 20mg twelve weeks after the diagnosis. Both patients had a steroid tapering time longer than that recommended and suffered from side effects. Side effects such as fluid retention, hypertension, hyperglycemia, gastro-intestinal bleeding, osteoporosis, myopathy and risk of infection are more vulnerable for elderly patients.

2) Intravenous immunoglobulin (IvIg)

Imbach et al\textsuperscript{21} first reported the successful use of pooled immunoglobulin for the treatment of acute ITP in paediatric patients in 1981. It resulted in a rapid rise in platelet counts within few days\textsuperscript{21}. Exact mechanism of action is uncertain. It is suggested that the rise in platelet count was due to competitive inhibition of the macrophage binding of platelets by preferential sequestration of immunoglobulin-coated red blood cells\textsuperscript{22}, thereby inducing a transient blockade of the macrophage system.

IvIg is recommended as initial treatment only for patients with platelet counts <50 x 10\textsuperscript{9}/L who have severe, life threatening bleeding. It should not be given to patients with platelet counts of 30 -100 x 10\textsuperscript{9}/L who are asymptomatic or have only minor purpura. Its role in long term therapy remains uncertain.

The adverse effects of IvIg are common but generally mild and self-limited, including headache, fever and chills. However, IvIg can increase blood viscosity and has been associated with cardiovascular or cerebrovascular thromboembolism. It should be used judiciously in elderly patients and patients with pre-existing vascular disease\textsuperscript{23}.

3) Splenectomy

Splenectomy, first performed in the 20's, was the earliest effective treatment for ITP before glucocorticoid therapy was introduced. Splenectomy removes the potential site of destruction of antibody-sensitized platelets and also results in a reduction of antibody production. Over 80\% of patients have platelet responses within several days, though some may only respond after 10 days\textsuperscript{24}. Approximately two thirds of adults will achieve a complete remission following splenectomy and will require no additional therapy\textsuperscript{12,25}. Younger age\textsuperscript{24,38} and short duration of disease\textsuperscript{24} are associated with better prognosis.

To minimize the risk of post-splenectomy sepsis, it is recommended that patients should be immunized with polyvalent pneumococcal vaccine, haemophilus influenza type b vaccine and quadrivalent meningococcal polysaccharide vaccine at least 2 weeks before surgery\textsuperscript{9}. The operative mortality is less than 1\% and peri-operative bleeding is rare in young adults. However, splenectomy, being a major surgery, should be cautiously considered in elderly patients as comorbidity conditions may complicate the operation. Recently, laparoscopic splenectomies have been increasingly performed for ITP especially in patients enfeebled by age or corticosteroid. It has the advantages of reduced morbidity and shortened stay in hospitals\textsuperscript{26}. Although rare, portal vein thrombosis has been reported following splenectomy\textsuperscript{27}.

4) Splenic irradiation and embolization

Therapeutic responses are also reported with splenic irradiation\textsuperscript{28,29} and partial splenic
embolization. Splenic irradiation can be an alternative option for older patients in whom the risk associated with splenectomy is high. Potential adverse effect is the production of adhesions surrounding the spleen, which may complicate subsequent splenectomy. Partial splenic embolization is also an alternative, although the complications associated with this procedure (fever, pain, nausea, perisplenic fluid, pleural effusion, splenic abscess or rupture) suggest that it should be considered only when all other alternatives have been exhausted.

5) Immunosuppressive agents

The use of immunosuppressive agents in ITP has been documented. They have been administered either alone or in combination with corticosteroid with variable success. Their use should be reserved for refractory cases of ITP.

a) Azathioprine

The use of azathioprine in adult chronic ITP was first reported in the 60's. The largest single review is that of Quinquandon et al in 1990. Platelet responses were observed in 64% and were complete in 45% of cases. The median time to achieve a response was 4 months. A trial of about 6 months is recommended. Rarely, the response may not occur until 10 months after treatment. Once a response is obtained, the dose should be tapered to the lowest level which results in a haemostatic platelet count. The potential adverse effects include leucopenia, secondary malignancy and teratogenicity. Relapse often occurs when the therapy is stopped. The combination of azathioprine and steroid may be synergistic, and allows a reduction in steroid dosage.

b) Cyclophosphamide

Studies showed that cyclophosphamide increased platelet counts in 60% of adult patients and 20% maintained normal platelet counts for 2-3 years after discontinuing treatment. Responses were seen more often in younger patients and in those with a shorter duration of disease. A trial of 3 months is needed although the usual response time is 6-8 weeks. Known adverse effects include bone marrow suppression, alopecia, haemorrhagic cystitis, infertility and secondary malignancy.

c) Vinca alkaloids

Vinca alkaloids may produce a transient increase in platelet counts lasting 1 to 3 weeks in two thirds of patients, but a sustained normal platelet count occurs in less than 10% of patients. They bind to platelet microtubules which permit the drugs to be delivered to tissue macrophages and thereby inhibit their phagocytic capabilities. It may take 7 to 10 days before there is a response. Potential adverse effects include neutropenia, fever, thrombophlebitis and peripheral neuropathy. Successful use of vincristine in elderly patients has also been reported. However, because of its propensity to produce debilitating neuropathy in the elderly, it should be used with caution.

6) Danazol

Danazol is a synthetic testosterone derivative. Its mechanism of action in treatment of ITP is uncertain. It may impair macrophage-mediated clearance of antibody-coated platelet initially, but inhibition of antibody production may account for its late effect. Although early reports suggested good response, other publications reflected disappointing results. Elderly patients and those splenectomized responded best to therapy; the lowest response rates occurred in younger nonsplenectomized women. Response time may take 2 to 6 months. Side effects are very unpleasant including weight gain, amenorrhoea, muscle cramps, myalgia, hirsutism, and rarely liver damage. Paradoxically, thrombocytopenia has been reported as a rare adverse effect of danazol.

7) Other treatments

Anti-D, an IgG fraction containing a high proportion of antibodies to the Rh(D) antigen of red blood cells, was first reported by Salama et al to be used for patients with ITP in mid-80's. Since then, there has been growing experience with the use of anti-D in the western societies. Its mechanisms of action are not completely understood, although they are similar to that of IVIG. It was proposed that intravenous infusion of anti-D into a D-positive recipient leads to antibody coating of circulating erythrocytes that are cleared primarily by the spleen. This immune-mediated clearance of sensitized erythrocytes occupies the reticuloendothelial system and allows survival of antibody-coated platelets. This mechanism requires the patient to be both Rh-positive and to have a functioning spleen. An expected side effect is, therefore, haemolytic anaemia. Other adverse events like headache, nausea, fever and chills which typically occur 1 to 2 hours after infusion are common. The indications for its use are similar to those for IVIG although one randomized study...
showed that IVIg offered a faster recovery of platelet count than anti-D. In general, anti-D has the advantages of IVIg (high efficacy rate, few side effects) but lacks some of its obvious disadvantages (long infusion time, high cost). The use of anti-D in Hong Kong is still yet to see.

Other than the agents mentioned above, some studies have been carried out to investigate the effectiveness of Dapsone, Alpha-interferon, ascorbic acid, plasma exchange, protein A immunoadsorption, colchicine, and cyclosporin in ITP. However, these treatments have received very limited evaluation and data supporting these treatment modalities is limited.

Conclusion
The incidence of ITP in older age group may be greater than commonly believed. Clinicians taking care of older adults must remain alert to the diagnosis of ITP. Since it is treatable and controllable, ITP should be considered seriously in the differential diagnosis of any patient with thrombocytopenia, irrespective of age. Severe bleeding episodes are more common in the elderly group. Early intervention is necessary.

Treatment options for the older adults are similar to that for young adults, so is the recommended dose of steroid. Besides steroid, splenectomy (preferably laparoscopic) is considered as a second line therapy if the elderly patient is surgically fit. Danazol can be considered for long term treatment because of its more favorable side effect profile as compared to steroid and immunosuppressive agents. Whether a smaller dose of steroid is equally effective in elderly patients remains to be studied. Side effects of treatment should be monitored during treatment.

References

WHENEVER I DRINK GUINNESS, I REMEMBER “STUDENT”

Earlier this century, a mathematician who worked for the Guinness Brewing Company in Dublin derived the distribution of the means of random samples from a Normal distribution. He called it t-distribution. He published his statistical papers under the pseudonym “Student”. His true name is W.S. Gossett. Now we call it “Student’s t distribution” in memory of him.

Next time, when you drink Guinness, think about Student’s t-distribution.