The aim of the study was to analyze causes, location and signs and symptoms of the upper extremity deep vein thrombosis (UEDVP) in twelve patients who were referred for tests for trombophilia; these patients were treated from 2002 to 2009 in various Clinics of Warsaw Medical University.

Material and methods. Retrospective analysis involved collection of clinical data of hospitalized patients related to signs and symptoms and location of the thrombosis, antithrombotic treatment and results of tests for thrombophilia. Patients with thrombosis caused by dialysis catheter, chemotherapy or paranteral nutrition and cardiac pacemaker electrode were excluded from the study.

Results. Eight of the study subjects had a primary thrombosis: in as many as five of them this was an exercise-induced thrombosis. Secondary thrombosis was diagnosed in four patients, two of whom had a malignancy, the third one used oral contraceptives while the fourth, pregnant patient, had UEDVP associated with ovarian hyperstimulation syndrome.

Conclusions. Pulmonary embolism (PE) without lower extremity thrombosis should prompt the search for UEDVT that can be asymptomatic. One of the study subjects underwent imaging studies that confirmed presence of thrombosis of the left brachiocephalic vein only after PE was detected. The study group contained many relatively young patients (five patients) with exercise-induced UEDVT, indicating possible thrombotic complications following too vigorous physical exercise. UEDVT that occurred in a pregnant patient was a complication of hormonal stimulation of ovaries used in the treatment of infertility. Pain and edema of the neck in such patients should prompt their attending physician to perform imaging studies. Should UEDVT be detected, antithrombotic heparin therapy should be started.

Key words: venous thrombosis, upper extremity deep vein thrombosis, trombophilia

Incidence of symptomatic upper extremity deep vein thrombosis (UEDVT) reported in the literature ranges from 4 to 10% of all deep vein thrombosis cases (1-5). However these data may be underestimated since UEDVT is often asymptomatic and pulmonary embolism is often its first manifestation (4, 6).

Most risk factors of lower extremity deep vein thrombosis also increases the risk of UEDVT although to a variable degree. The most common predisposing factors to upper extremity deep vein thrombosis include foreign body in the vessel lumen (vascular catheter and sometimes cardiac pacemaker electrode) and active malignancy (1, 2, 5, 7-11). Congenital thrombophililia is detected much less often in patients with upper than in lower extremity deep vein thrombosis (5, 12, 13, 14).

Upper extremity thrombosis may also be caused by intensive physical exercise. In 1875 Paged in England and then in 1884 Schrötter in Germany were the first to report subclavian or axillary vein thrombosis after very dynamic physical exercise. This thrombosis, currently referred to as exercise-induced thrombosis, may be caused e.g. by weight lifting, rowing, wrestling (10, 15, 16, 17). Currently it is recognized that exercise-induced thrombosis is furthermore favored by anatomical anomalies. These anomalies, referred to as upper chest opening syndrome, were found in 4%
patients with UEDVT (12). They affect bones (abnormal structure of the first rib or clavicle), tendons (additional connective tissue bands) or muscles in the region where veins that drain the upper extremity are located (scalenum anterior muscle and pectoris minor muscle) and result in slowing of blood flow through mechanical compression of the blood vessels (15, 17). Exercise-induced thrombosis of the subclavial and/or axillary vein in patients with anatomical anomalies is referred to as Paget-Schrötter syndrome (15, 16). Exercise-induced thrombosis with or without accompanying anatomical anomalies and essential thrombosis are termed primary UEDVT. Thrombosis caused by risk factors, including the most common catheter and active malignancy, is termed secondary thrombosis and accounts for approximately 80% of all UEDVT cases (4, 18, 19).

UEDVT complications – similarly as for lower extremity thrombosis – are not limited to pulmonary embolism, but also manifest as chronic, thrombosis-induced venous insufficiency and recurrent thrombosis; furthermore they may result in loss of vascular access (5, 9, 11, 17, 18, 20, 21, 22).

The aim of this study was to analyze causes, location and signs and symptoms of UEDVT in twelve patients who were referred for tests for trombophilia; these patients were treated from 2002 to 2009 in various clinics of Warsaw Medical University (MUW).

MATERIAL AND METHODS

From 2002 to 2009, 12 patients (6 women and 6 men) with UEDVT, aged 18 to 58 years (average age 36 years) were hospitalized in various clinics of MUW (Department of General, Vascular and Transplantation Surgery; Department of General and Thoracic Surgery; Department of General, Gastroenterological and Oncological Surgery; Department of Hematology, Oncology and Internal Medicine; Department of Internal Medicine and Endocrinology; Department of Gastroenterology and Metabolic Disease) and were referred for tests for trombophilia. Patients with thrombosis caused by dialysis catheter, chemotherapy or paranteral nutrition and cardiac pacemaker electrode were excluded from the study. The thrombosis was diagnosed basing on imaging studies (US imaging, possibly CT), performed by radiologists.

Complete blood cell count, fibrinogen concentration (colorimetric method), factor II, V and VII activity (one-step coagulometric methods), D-dimer concentration (ELISA, bioMérieux, VIDAS D-dimer) were analyzed in all patients. Tests for trombophilia included: activity of antithrombin and protein C (amidolytic metod), resistance to active protein C (coagulometric method), and tests for lupus anticoagulant (coagulometric method).

RESULTS

Patient characteristics presented in tab. 1 indicates that eight patients developed UEDVT without detected risk factors (malignancy, pregnancy, vascular catheter, trombophilia). It was related to intensive physical exercise in five of them (bodybuilding, parachute jumping). Furthermore, thrombosis was diagnosed in four subjects: two of them had an active malignancy, the third one used oral contraceptives while the fourth patient was 11 weeks pregnant: her twin pregnancy was a result of in vitro conception preceded by hormonal stimulation of ovaries.

The thrombosis occurred in the right extremity in seven of twelve patients. Neither patient was found to have a bilateral thrombosis. Most commonly the thrombosis was located in the subclavian vein, followed by the axillary vein, brachial veins and jugular vein (tab. 1). More than one venous segment was affected by thrombosis in three patients.

UEDVT was documented by ultrasound (US) imaging in nine patients. Results of US imaging in one patient were inconclusive and UEDVT was confirmed by computed tomography imaging. UEDVT was diagnosed using computed tomography imaging, without US imaging, in two patients (tab. 1). Neither patient required venography to confirm thrombosis.

Lupus anticoagulant, antithrombin deficiency, protein C deficiency or resistance to an active protein C were found in none of the twelve patients.

Table 2 summarizes other coagulation tests. Thrombocytosis was found only in one patient L.E. who had undergone hormonal stimulation of ovaries. She was found to have an increased activity of clotting factors II, V and VII and increased fibrinogen concentration. Fibrino-
Patients with upper extremity deep vein thrombosis was also found in two patients with malignancy (G.B., K.W.) and in one patient with exercise-induced thrombosis (P.P.). Increased D-dimer concentration, suggesting fibrinolytic degradation of intravascular fibrin deposits, was found in eight patients. Normal D-dimers were found in four patients who were receiving treatment with low molecular weight heparin (LMWH).

All study patients received LMWH during their hospitalization according to Polish recommendations of treatment of lower extremity thrombosis, valid at the time of patient hospitalization. At discharge, five patients were advised to continue antithrombotic treatment with LMWH for three to six months while the pregnant patient (Ł.E.) was advised to continue her treatment until the end of her pregnancy. Five patients had an oral antagonist of vitamin K implemented during their hospitalization, under INR guidance, and advised to continue their treatment for at least three months. One patient with mild thrombosis was discharged and advised to take acetylsalicylic acid (2 mg/kg).

**DISCUSSION**

Currently there is no established definition of UEDVT, however it is generally believed to refer to thrombosis of subclavian, axillary and less often brachial vein as well as internal jugular vein. Vascular catheter is the most common cause of UEDVT. Patients with dialysis catheter, receiving chemotherapy or parenteral nutrition, were excluded from the study group. Therefore, secondary thrombosis rate was much lower than reported in the literature (4, 18, 19). However, a group of patients with exercise-induced UEDVT is clearly overrepresented in our study population versus literature data, which is the result of patient selection method used.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Thrombosis location</th>
<th>Signs and symptom sof the thrombosis</th>
<th>Diagnostic procedures</th>
<th>Risk factors</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>W.A.</td>
<td>34</td>
<td>F</td>
<td>left subclavian vein</td>
<td>pain, edema</td>
<td>TK / CT</td>
<td>none detected</td>
<td>nadroparin 170 IU/kg every 24 h</td>
</tr>
<tr>
<td>R.A.</td>
<td>34</td>
<td>F</td>
<td>right subclavian vein</td>
<td>pain, edema, redness</td>
<td>USG, TK / US CT</td>
<td>oral contraception, cigarette smoking</td>
<td>enoxaparin 1 mg/kg every 12 h</td>
</tr>
<tr>
<td>K.J.</td>
<td>30</td>
<td>M</td>
<td>right axillary vein</td>
<td>pain, edema</td>
<td>USG / US</td>
<td>none detected</td>
<td>nadroparin 170 IU/kg every 24 h</td>
</tr>
<tr>
<td>W.K.</td>
<td>18</td>
<td>M</td>
<td>right axillary vein</td>
<td>pain, edema</td>
<td>USG / US</td>
<td>vigorous exercise</td>
<td>nadroparin IU/kg every 24 h</td>
</tr>
<tr>
<td>P.P.</td>
<td>26</td>
<td>M</td>
<td>right subclavian, axillary and brachial vein</td>
<td>pain, edema</td>
<td>USG / US</td>
<td>vigorous exercise</td>
<td>enoxaparin 1,5 mg/kg every 12 h</td>
</tr>
<tr>
<td>G.T.</td>
<td>44</td>
<td>M</td>
<td>right subclavian vein</td>
<td>pain, edema</td>
<td>USG / US</td>
<td>none detected</td>
<td>enoxaparin 1,5 mg/kg every 12 h</td>
</tr>
<tr>
<td>Ł.E.</td>
<td>37</td>
<td>F</td>
<td>left subclavian vein, left internal jugular vein</td>
<td>pain, edema</td>
<td>USG / US</td>
<td>11 weeks gestation, ovarian hyperstimulation syndrome</td>
<td>enoxaparin 1 mg/kg every 12 h</td>
</tr>
<tr>
<td>G.B.</td>
<td>44</td>
<td>F</td>
<td>left axillary, brachial veins</td>
<td>pain, edema</td>
<td>USG / US</td>
<td>acute myelogenous leukemia, 2- u phenotypic</td>
<td>enoxaparin 1 mg/kg every 12 h</td>
</tr>
<tr>
<td>P.K.</td>
<td>22</td>
<td>F</td>
<td>left subclavian vein</td>
<td>pain, edema, cyanosis</td>
<td>USG / US</td>
<td>vigorous exercise</td>
<td>nadroparin 170 IU/kg every 24 h</td>
</tr>
<tr>
<td>W.K.</td>
<td>45</td>
<td>M</td>
<td>right subclavian vein</td>
<td>pain, edema</td>
<td>USG / US</td>
<td>parachute jumping</td>
<td>nadroparin 170 IU/kg every 24 h</td>
</tr>
<tr>
<td>W.K.</td>
<td>53</td>
<td>M</td>
<td>left brachiocephalic vein</td>
<td>asymptomatic, pe</td>
<td>TK / CT</td>
<td>(metastatic) pancreatic cancer</td>
<td>enoxaparin 1 mg/kg every 12 h</td>
</tr>
<tr>
<td>S.B.</td>
<td>36</td>
<td>F</td>
<td>right subclavian vein</td>
<td>pain, edema</td>
<td>USG / US</td>
<td>vigorous exercise</td>
<td>nadroparin 170 IU/kg every 24 h</td>
</tr>
</tbody>
</table>
A limitation of this study is lack of comprehensive tests to detect a superior chest opening syndrome in patients with exercise induced thrombosis.

A female Ł.E. with subclavian vein and internal jugular vein thrombosis in 11 weeks gestation (twin pregnancy) is an interesting and rare case in our study population. The patient had been treated for infertility with hormonal stimulation of ovaries and then underwent in vitro fertilization. A consulting gynecologist, after performing additional tests, diagnosed the patient with a mild ovarian hyperstimulation syndrome. After two weeks of treatment with LMWH, pain and edema of the extremity resolved and the patient was discharged home and advised to continue LMWH therapy until the end of her pregnancy.

Jugular and subclavian vein thrombosis, found in patient Ł.E., is one of the complications of hormonal stimulation of ovaries, used in the treatment of infertility. This thrombosis is a consequence of ovarian hyperstimulation syndrome that occurs in 2-6% of the treated women (23, 24). This syndrome manifests as enlarged ovaries, massive ascites, pleural fluid and hemoconcentration (23-31). Hemoconcentration is caused by hypovolemia resulting from excessive blood vessel permeability mediated by rennin-angiotensin system activation (28). Patients with ovarian hyperstimulation syndrome were reported to have a tendency toward thrombocytosis that could facilitate thrombosis, increased concentration of fibrinogen and factor V and excess of fibrinolysis inhibitors (32). The patient Ł.E. had thrombocytosis, increased fibrinogen concentration and increased activity of clotting factors II, V and VII (tab. 2). However, these changes do not account for hormonal ovary stimulation predisposing to the upper extremity thrombosis instead of lower extremity thrombosis. According to Bauersachs et al. (31), high estrogen concentration is found in the peritoneal fluid in ovarian hyperstimulation syndrome. These estrogens then migrate through lymphatic system, via thoracic duct, back to the venous system of the upper extremities, resulting in local activation of coagulation.

Venous thrombosis accompanying infertility treatment is located almost exclusively in upper extremities and manifests – as in patient Ł.E. – a few weeks after resolution of ovarian hyperstimulation syndrome (23, 26-29). The thrombosis is more commonly found in the jugular vein than in subclavian veins, but the reason behind it remains unknown (29).

Recently the number of women who use the assisted reproduction has markedly increased, which is reflected by increased number of publications on the thrombotic complications that accompany this method. Therefore, there have been suggestions that severe or moderate ovarian hyperstimulation syndrome should be an indication to thrombotic prophylaxis for 1 – 2 months after symptom resolution (30). However, neck pain and edema should make the affected woman looking for imaging studies to

<table>
<thead>
<tr>
<th>Patient</th>
<th>fibrynogen (mg/dl)</th>
<th>Clotting factor</th>
<th>D-dimer (ng/ml)</th>
<th>Blond platelets (x10^3/μl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>W.A.</td>
<td>325</td>
<td>111</td>
<td>124</td>
<td>97</td>
</tr>
<tr>
<td>R.A.</td>
<td>310</td>
<td>114</td>
<td>103</td>
<td>104</td>
</tr>
<tr>
<td>K.J.</td>
<td>305</td>
<td>117</td>
<td>109</td>
<td>90</td>
</tr>
<tr>
<td>W.K.</td>
<td>280</td>
<td>98</td>
<td>91</td>
<td>78</td>
</tr>
<tr>
<td>P.P.</td>
<td>515</td>
<td>120</td>
<td>80</td>
<td>102</td>
</tr>
<tr>
<td>G.T.</td>
<td>345</td>
<td>104</td>
<td>106</td>
<td>99</td>
</tr>
<tr>
<td>Ł.E.</td>
<td>545</td>
<td>144</td>
<td>126</td>
<td>135</td>
</tr>
<tr>
<td>G.B.</td>
<td>500</td>
<td>145</td>
<td>154</td>
<td>92</td>
</tr>
<tr>
<td>P.K.</td>
<td>250</td>
<td>89</td>
<td>76</td>
<td>65</td>
</tr>
<tr>
<td>W.K.</td>
<td>360</td>
<td>90</td>
<td>147</td>
<td>98</td>
</tr>
<tr>
<td>W.K.</td>
<td>795</td>
<td>119</td>
<td>166</td>
<td>100</td>
</tr>
<tr>
<td>S.B.</td>
<td>290</td>
<td>107</td>
<td>100</td>
<td>96</td>
</tr>
<tr>
<td>Normal range</td>
<td>220-376</td>
<td>70-120</td>
<td>70-120</td>
<td>&lt;500</td>
</tr>
</tbody>
</table>
explain whether jugular or subclavian vein thrombosis is the cause for the above mentioned signs and symptoms (27, 28). In the event of documented UEDVT, antithrombotic heparin therapy (29) should be started immediately and continued until the end of her pregnancy. The patient Ł.E. was managed in such manner.

Clinical characteristics of patients with UEDVT and lower extremity deep vein thrombosis differ. Patients with upper extremity thrombosis are younger, have lower body weight and less often have a family history of thrombotic disease (5). Patients with UEDVT analyzed by us were relatively young (average and 36 years) and were not overweight; only one study subject was a cigarette smoker.

According to the literature, the most common signs and symptoms of UEDVT include: edema (82% of patients) and pain (37% of patients) of the extremity and sometimes neck and shoulder erythema and edema, cyanosis of the extremity (2, 11, 17, 18). Due to the fact that these signs and symptoms in approximately 50% of patients are not caused by UEDVT, differential diagnostics is often required (11, 21), including superficial vein thrombosis, cellulitis, lymphatic edema and local disease conditions that result in secondary thrombosis (e.g. malignant infiltrate around a vein, fibro-muscular hypertrophy of venous walls). Eleven of our study subjects presented with both pain and edema of the extremity. Furthermore, edema and cyanosis of the extremity occurred in two patients. The twelfth patient developed pulmonary embolism caused by asymptomatic UEDVT (tab. 1).

Pulmonary embolism (PE) is a life threatening complication of UEDVT. Symptomatic PE is definitely less common in patients with upper than lower extremity thrombosis (5). One of the study subjects (Z.P.) developed respiratory insufficiency caused by P.E., confirmed both by computed tomography imaging as well as by subsequent autopsy. Asymptomatic thrombosis of the left brachiocephalic vein was the cause of this thrombosis. The patient died of multiorgan failure caused by metastatic malignancy. Example of this patient supports literature reports that pulmonary embolism is often the first sign of UEDVT (4, 6).

Currently, most common diagnostic procedure used to demonstrate thrombosis, is US imaging with vein compression tests often accompanied by flow examination using Doppler imaging. On the other hand, computed tomography imaging is used to assess lumen of thoracic veins. Venography is the ultimate study – considered as a gold standard (33).

Upper extremity deep vein thrombosis most often affects the subclavian vein, followed by axillary, brachial and other upper extremity veins, usually affecting simultaneously more than one venous segment (11, 12). In patients with UEDVT hospitalized in MUW clinics, the thrombosis most often affected the subclavian vein (8/12 patients), followed by axillary vein (4/12 patients), brachial veins (2/12 patients) and brachiocephalic vein in one case. The thrombosis affected more than one venous segment in three patients. Thrombosis developed slightly more often in the right extremity (seven cases) and there was no bilateral thrombosis in our study.

Studies of congenital thrombophilia in patients with UEDVT are very limited. Linnermann et al. compared a series of 150 patients with the upper extremity thrombosis from a single-site register MAISTHRO with a group of 300 patients with the lower extremity thrombosis, matched for gender and age (12). Thrombophilia was found in 55% of patients with the lower extremity thrombosis and only in 34% of patients with UEDVT which may account for less common family history of thrombosis in these patients (2, 12). We did not find lupus anticoagulant or antithrombin deficiency, protein C deficiency or resistance to active protein C in our study subjects. However, we did not assay activity of protein S inhibitor or prothrombin gene mutations (G 20210 A).

Since no prospective, comparative studies are available (due to difficulties in enrollment of large number of patients), there is no consensus with regard to optimal antithrombotic treatment of UEDVT. Joffe et al. analyzed risk factors in the largest group of 592 patients with UEDVT did not present long-term results of treatment (2). According to ACCP (American College of Chest Physicians) suggestions updated periodically, patients with UEDVT should receive the same treatment as patients with lower extremity thrombosis. However, a large retrospective study by Spencer et al. (7) demonstrated that only 56 per cent of patients received antithrombotic treatment following their discharge from a hospital. This may re-
fect quite common belief that the upper extremity thrombosis does not require long-term anticoagulation (1). All our hospitalized study subjects received LMWH treatment at therapeutic doses, according to Polish guidelines of prophylaxis and treatment of thromboembolic disease. Gradual resolution of complaints was noted in eleven patients while one patient died for multiorgan failure resulting from metastatic pancreatic cancer. At discharge the patients were advised to continue their antithrombotic treatment for at least three months. Five patients were to continue LMWH treatment and another five were advised to continue their treatment with oral vitamin K antagonists. One patient (W.K.) with mild thrombosis—who furthermore did not consent to any of the above mentioned therapies—was discharged home and advised to take acetylsalicylic acid at a dose of 2 mg/kg every 24 hours. The decision of a clinician with regard to antithrombotic treatment of patients with upper extremity thrombosis often is additionally dictated by the presence of malignancy. In RIETE (1) study, patients with UEDVT, following initial LMWH treatment, received long-term LMWH treatment if they had a malignancy (75% of patients) or at least three months of vitamin K antagonist treatment if they had no malignancy (76% of patients).

ACCP recommends avoidance of thrombolysis and surgical procedures in most of UEDVT patients due to numerous possible complications (34). Patients with Paget-Schröter are an exception to this rule because antithrombotic treatment preceded by thrombolysis is often successful in these patients. However, further surgical procedures in these patients are dependent on the type of detected anatomical anomaly (16).

CONCLUSIONS

1. Pulmonary embolism (P.E.) without lower extremity thrombosis should prompt the search for UEDVT that can be asymptomatic. One of the study subjects (with malignancy) underwent imaging studies that confirmed presence of thrombosis of the left brachiocephalic vein only after P.E. was detected.
2. The study group contained many relatively young patients (five patients) with exercise-induced UEDVT, indicating possible thrombotic complications following too vigorous physical exercise.
3. UEDVT that occurred in a patient at 11 weeks gestation (twin pregnancy) was a complication of hormonal stimulation of ovaries used in the treatment of infertility. Pain and edema of the neck in such patients should prompt their attending physician to perform imaging studies. Should UEDVT be detected, antithrombotic heparin therapy should be started and continued until the end of the pregnancy what was the case in our patient.
4. Currently there is no consensus with regard to optimal antithrombotic treatment of UEDVT. All study subjects with UEDVT received LMWH during their hospitalization, according to Polish guidelines of treatment of the lower extremity thrombosis.

Acknowledgements. We would like to thank heads of individual clinics of MUW for their consent to the access to medical records of the discussed patients and to publish data contained in them.

PIŚMIENNICTWO / REFERENCES