بسم الله الرحمن الرحيم

Ain Shams University Information Network

جامعة عين شمس

شبكة المعلومات الجامعية

@ ASUNET

# شبكة المعلومـــات الجامعية

# التوثيق الالكتروني والميكروفيلم

شبكة المعلومات الجامعية

# جامعة عين شمس

## التوثيق الالكتروني والميكروفيلم

## قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأفلام قد اعدت دون آية تغيرات

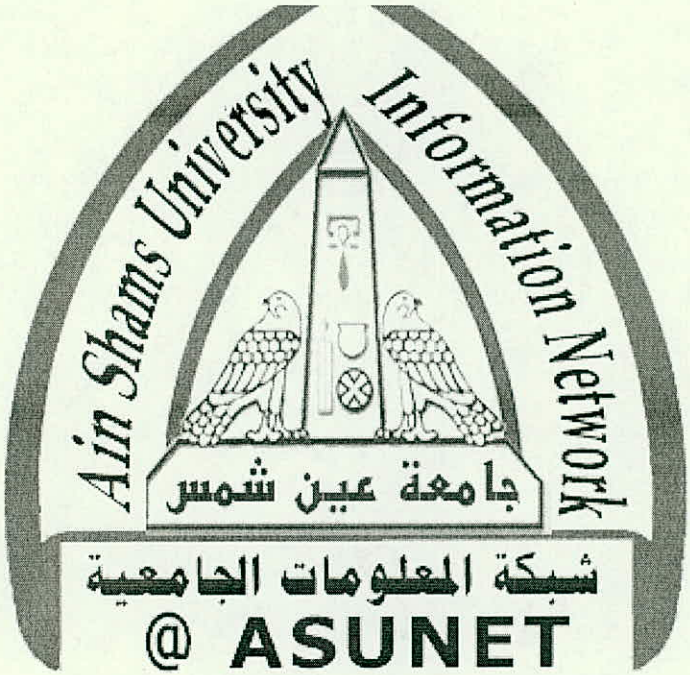
Ain Shams University Information Network
جامعة عين شمس
شبكة المعلومات الجامعية
@ ASUNET

## يجب أن

تحفظ هذه الأفلام بعيداً عن الغبار

في درجة حرارة من 15 – 20 مئوية ورطوبة نسبية من 20-40 %

**To be kept away from dust in dry cool place of**
**15 – 25c and relative humidity 20-40 %**




# بالرسالة صفحات

# لم ترد بالأصـــل


شبكة المعلومات الجامعية


# بعض الوثائق الأصلية تالفة

# ACQUIRED von WILLEBRAND DISEASE (AvWD) IN HAEMATOLOGIC MALIGNANCIES

*Thesis*

Submitted for Partial Fulfillment of
M.D. Degree in
***The Laboratory Medical Oncology***

*By*

**Walid Monir Ahmed**
M. B. B. Ch. & M. Sc.

*Supervised By*

**Prof. Dr.**
**Magda Mahmoud Assem**
*Professor of Clinical pathology*
*NCI, Cairo University*

**Prof. Dr.**
**Naguib Zoheir Mostafa**
*Professor of Clinical pathology*
*Cairo University*

**Dr. Maha Saleh**
*Fellow of Clinical pathology*
*NCI, Cairo University*



*National Cancer Institute*
CAIRO UNIVERSITY
2000

بسم الله الرحمن الرحيم

﴿ وَقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ ﴾

صدق الله العظيم

[ التوبة : ١٠٥]

# ABSTRACT

Acquired von Willebrand disease (AvWD) is an acquired bleeding disorder which may suddenly become manifest in individuals, usually in the absence of a personal or family history of bleedings and frequently in association with monoclonal gammopathies, lymphoproliferative, myeloproliferative and autoimmune disorders. In a minority of the cases AvWD may develop in association with drugs or solid tumors. Pathogenetic mechanisms involve autoantibodies directed against von Willebrand factor (vWF) resulting in a rapid clearance of vWF from the circulation and/or release of vWF from storage sites; or precipitation of plasma vWF. Treatment options include-whenever possible-treatment of the underlying disorder or symptomatic treatment aimed at replacing the loss of vWF by either infusion of vWF-rich concentrates or administration of desmopressin (DDAVP). In related cases with anti-vWF antibodies, administration of high-dose intravenous gammaglobulin, plasma exchange or extracorporeal immuno-adsorption may be successful. This study included 114 patients (73 males and 41 females) and 10 controls. The age of the patient group were ranging from 15-65 years while the age of the control group were ranging from 20-65 years. The patient group were presented to NCI complaining of a recent development of non-thrombocytopenic mucocutaneous bleeding due to malignant haematological disorder. These patients were subdivided according to their diagnoses into: CML (34 cases), CLL (26 cases), NHL (25 cases), MM (19 cases), HD (6 cases) and MDS (4 cases). All patients and control groups were subjected to: Complete physical and clinical examination, laboratory work up including: BT, CBC, blood grouping, serum total protein, APTT, vWF: Ag, vWF: Ri Cof activity, F VIII:C and Multimer Analysis.

**Key words:** Von Willebrand factor; acquired von Willebrand disease; von Willebrand disease.

# Acknowledgement

*I am deeply grateful to* ***Prof. Dr. Magda Assem,*** *Professor of Clinical pathology, NCI, Cairo University, for her kind help and persistent assistance and encouragement bringing this work to light. She spent much of her valuable time in revising every word in this thesis.*

*My gratitude and thanks to* ***Prof. Dr. Mohamed Naguib Zuhair,*** *Professor of Clinical pathology, NCI, Cairo University, for his valuable help during the progress of this work.*

*I would not forget the help, support and encouragement by* ***Dr. Maha Saleh,*** *Fellow of Clinical pathology, NCI, Cairo University.*

*I would like to express my sincere appreciation and thanks to* ***Prof. Dr. Samya Akle,*** *Prof. of Clinical Pathology, NCI, Cairo University, for her valuable help in performing von Willebrand antigen test.*

*I am thankful to* ***Prof. Dr. Nelly Hassan,*** *NCI, Cairo University, for her kind assistance in the statistical analysis of results.*

*I would like to thank* ***Dr. Ibrahim Abdel Salam,*** *Associated Prof. of Molecular Oncology Department, NCI, Cairo University. Also, thanks to* ***Dr. Mohamed Mohamed Aly,*** *Lecture of Molecualr Oncology Department, NCI, Cairo University, they provide me a supported help in performing Multimer Analysis.*

*My deep gratitude to* ***Dr. Mohamed Hassan,*** *Associated Dr. of Clinical Pathology, Military medical Academy, Maadi Hospital, who was the pace-maker that pushed and directed my efforts while doing this work.*

*Last but not least, I am indebted to my father, my wife and my sister for their loving, kindness and ultimited support.*

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADP | Adenosine di-phosphate |
| AHF | Antihemophilic factor |
| AIHA | Autoimmune hemolytic anemia |
| ALL | Acute lymphoblastic leukemia |
| AML | Acute myeloblastic leukemia |
| AMM | Agnogenic myeloid metaplasia |
| APC | Activated protein C |
| APL | Acute promyelocytic leukemia |
| APTT | Activated partial thromboplastin time |
| ATIII | Antithrombin III |
| AvWD | Acquired von Willebrand disease |
| BT | Bleeding time |
| C4bp | C4-binding protein |
| CLL | Chronic lymphoid leukemia |
| CML | Chronic myeloid leukemia |
| CNS | Central nervous system |
| DDAVP | 1-deamino-8-D arginine vasopressin |
| DIC | Dissiminated intravascular coagulation |
| DMD | Direct mutation detection |
| DNA | Deoxyribonucleic acid |
| DS | Dermatan sulfate |
| EACA | ε-aminocaproic acid |
| EGF | Epidermal growth factor |
| EPCR | Endothelial cell protein C receptor |
| EPO | Erythropoietin |

| | |
|---|---|
| F VIII:C | Factor VIII coagulant |
| FDP | Fibrin degradation products |
| FPA | Fibrinopeptide A |
| FSF | Fibrin-stabilizing factor |
| GAG | Sulfated glycosaminoglycans |
| GP | glycoprotein |
| HC II | Heparin cofactor II |
| HCL | hairy cell leukemia |
| HD | Hodgkin's disease |
| HES | Hydroxyethyl starch |
| HLA | Human leukocyte antigen |
| HMWK | High-molecular weight kininogen |
| IL | Interleukin |
| ITP | Idiopathic thrombocytopenic purpura |
| Kb | Kilobase |
| KD | Kilodalton |
| LACI | Lipoprotein associated coagulation inhibitor |
| LDL | Low-density lipoprotein |
| LRP | Low-density lipoprotein receptor-related protein |
| MM | Multiple myloma. |
| MMP | Matrix metalloproteinase |
| MPD | Myeloproliferative desease |
| mRNA | messenger-ribonucleic acid |
| NHL | Non-Hodgkin's lymphoma |
| PA | Plasminogen activator |
| PAI | Plasminogen activator inhibitor |
| PAR | Plasminogen activator receptor |
| PCR | Polymerase chain reaction |

| | |
|---|---|
| PF-4 | Platelet factor 4 |
| PS | Protein S |
| PTA | Plasma thromboplastin antecedent |
| PTC | Plasma thromboplastin component |
| PV | Polycythemia vera |
| RFLP | Restriction fragment length polymorphism |
| r-FVIII | Recombinant factor VIII |
| Ri:cof | Ristocetin cofactor |
| RIPA | ristocetin-induced platelet agglutination |
| scu-PA | Singlechain urokinaase-type PA |
| Tf | Tissue factor |
| TFPI | Tissue factor pathway inhibitor |
| TIMPs | Tissue inhibitors of MMPs |
| TM | Thrombomodulin |
| t-PA | Tissue-type plasminogen activator |
| UHG | Universal heteroduplex generator |
| U-PA | Urokinase-type plasminogen activator |
| NSAID | Non-steroidal anti-inflammatory drug |
| vWD | von Willebrand disease |
| vWF | von Willebrand factor |
| vWF:Ag | von Willebrand factor antigen |