Issue: April - June 2023

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PATHOLOGY MATTERS

Bringing you the latest news in clinical testing

Laboratory Studies in Disseminated Intravascular Coagulation

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Disseminated intravascular coagulation (DIVC) is an acquired syndrome characterized by systemic activation of blood coagulation, which results in generation and deposition of fibrin, leading to microvascular thrombi (Figure 1) in various organs and contributing to multiple organ dysfunction syndrome. Consumption of clotting factors and platelets in DIVC can result in life-threatening haemorrhage. DIVC can result from numerous clinical conditions, including sepsis, trauma, obstetric emergencies, and malignancy.

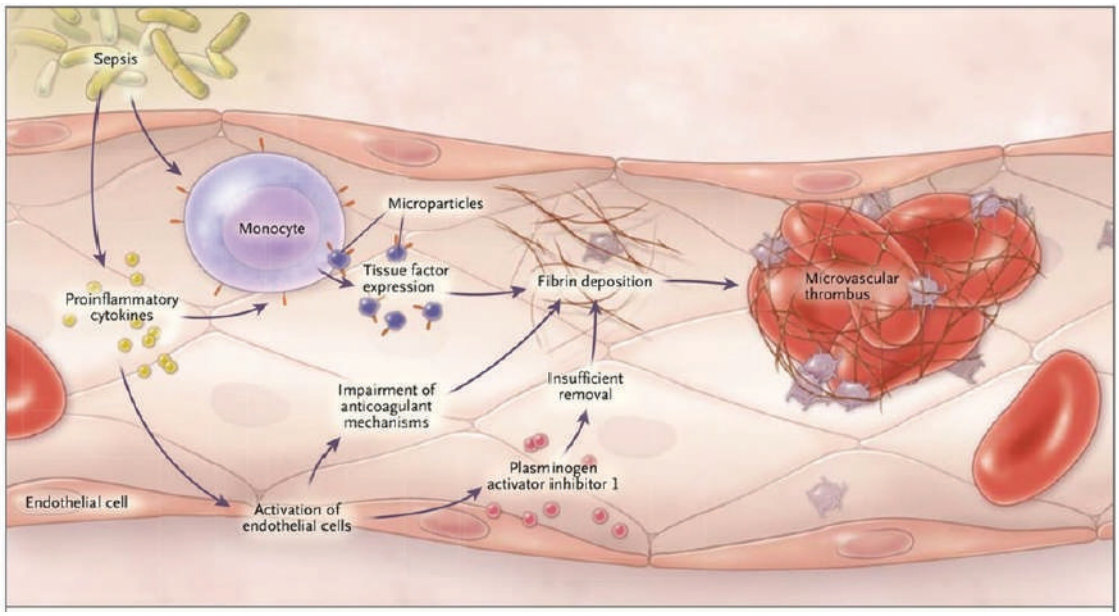

Figure 1: Pathogenesis of DIVC in sepsis

Clinical presentation: The clinical severity of DIVC varies such that DIVC may result:

1) in laboratory abnormalities only
2) renal dysfunction, hepatic dysfunction, respiratory dysfunction, shock and CNS dysfunction
3) in severe cases, massive haemorrhage or thrombosis.
    a. Haemorrhage, which is secondary to the consumption of coagulation factors and excessive fibrinolysis, occurs more commonly than thrombosis, occurring in 70–90% of patients.
    b. Thrombosis, which is secondary to activation of coagulation factors and platelet activation resulting in both microvascular thrombosis and large-vessel thrombosis, is less common, occurring in 10–40% of patients.

DIVC screening test should include:

1) Full blood count to look for thrombocytopenia
2) Peripheral blood film to look for schistocytes due to thrombotic microangiopathy (Figure 2)
3) Prolongation of activated partial thromboplastin time (aPTT) due to deficiency of intrinsic pathway coagulation factors such as FXI, FIX, FVIII and/or deficiency of common pathway coagulation factors such as FX, FV, FII, FI
4) Prolongation of prothrombin time (PT) due to deficiency of extrinsic pathway coagulation factor such as FVII and/or deficiency of common pathway coagulation factors such as FX, FV, FII, FI
5) Fibrinogen to look for fibrinogen deficiency
6) Elevated D-dimer level due to intense fibrinolytic activity (Figure 3)
7) Thrombin time (TT). TT measures the time to conversion of fibrinogen to fibrin. Decreased concentrations of fibrinogen, decreased clearance of fibrin degradation products and the presence of heparin prolong the thrombin time.

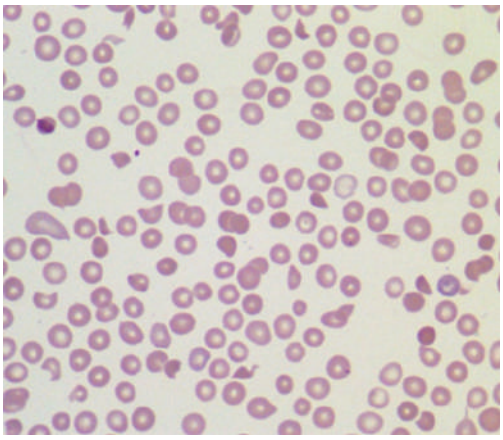

Figure 2: Schistocytes in blood film

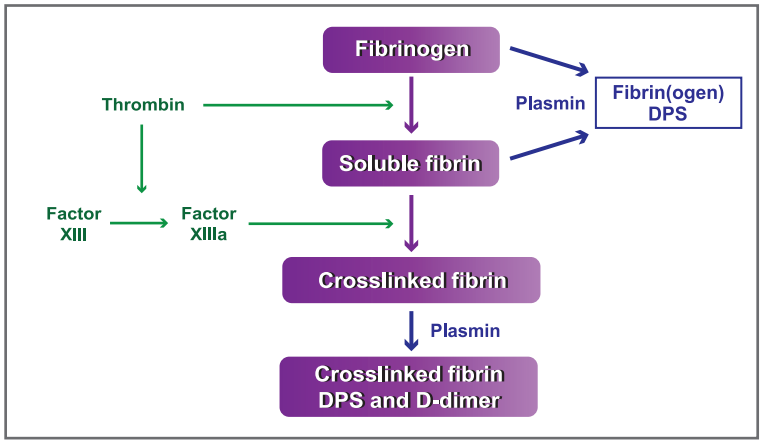

Figure 3: D-dimer formation

Diagnosis

The diagnosis of DIVC should encompass both clinical and laboratory information. Single test alone should not be used to screen for DIVC. It is essential to keep in mind that laboratory values may represent only a momentary glimpse into a very rapidly changing systemic process. It is important to repeat the tests to monitor the dynamically changing scenario based on laboratory results and clinical observations.

Principle of Management

Patients with DIVC should be treated at hospitals with appropriate critical care and subspecialty expertise, such as haematology, blood bank, or surgery. Key to the treatment of DIVC is the specific and vigorous treatment of the underlying disorder. In many cases the DIVC will spontaneously resolve when the underlying disorder is properly managed. Blood product such as platelet concentrate, fresh frozen plasma or cryoprecipitate should be directed not at simply correcting laboratory abnormalities but at addressing clinically relevant bleeding or meeting procedural needs. Heparin should be provided to those patients who demonstrate extensive vascular thrombosis without evidence of substantial haemorrhage.

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The Role of Diabetes-Associated Autoantibodies in Confirming the Diagnosis of Type 1 Diabetes Mellitus in Children and Adolescents

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Type 1 diabetes mellitus (T1DM) is a chronic condition caused by immune cell infiltration and destruction of the pancreas insulin-producing beta (β) cells. The death of β cells causes the loss of insulin secretion, causing hyperglycaemia. The Malaysian Diabetes in Children and Adolescents Registry published a report in 2007 stating that almost 70% of childhood and adolescent diabetes were T1DM patients[1].

Although T1DM is a metabolic disease, diabetes-associated autoantibodies (DAA) have been one of the markers used to confirm the diagnosis of T1DM. The Clinical Practice Guidelines recommended DAA testing, namely glutamic acid decarboxylase antibody (GADA), anti-islet antibody (ICA), insulin autoantibodies (IAA), protein tyrosine phosphatase antibody (IA-2A) and zinc transporter 8 autoantibody (ZnT8), to confirm T1DM diagnosis[2].

Despite DAA is a vital marker to confirm the diagnosis of T1DM, there are several limitations to using DAA in T1DM diagnosis. An American study reported 86% of children and adolescents with T1DM were positive for DAA (GADA, IAA and IA-2A), while 6% of Type 2 diabetes mellitus (T2DM) patients were positive for DAA[3]. Furthermore, 0.98% of young T2DM patients were positive with ZnT8[4], indicating that a positive titre of DAAs may not be diagnostic of T1DM. Another limitation of using DAAs is not all T1DM patients are positive for DAAs. These patients are autoantibody negative T1DM patients. 5.2% of young T1DM patients display no positive titre of DAAs[3]. At the same time, a study from Malaysia reported that 32% of young diabetes patients were seronegative despite being presented with the near or total destruction of β cells[5]. Therefore, the patient's history, blood glucose profile, glycated haemoglobin (HbA1c), DAA and possibly C-peptide levels are crucial before confirming a T1DM diagnosis.

Innoquest Pathology offers:

Panel Code	Tests	Specimen Requirements
GDA	GAD Autoantibodies	8ml Plain (Gel-YELLOW)
IAN	IA-2 Autoantibodies	8ml Plain (Gel-YELLOW)

References:

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Transforming Cancer Diagnosis and Treatment through Genomics

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Until a few years ago most cancer patients were being treated globally with the help of empirical, or “trial and error” medicine. Empirical medicine produces a relatively poor rate of drug response in many cancer patients with serious complications. Most patients suffered serious side effects with chemotherapy, with some not even able to recover from the debilitating aftereffects of prolonged treatment.

The new paradigm of personalised medicine is breaking that cycle of “trial and error” medicine by considering the precise genetic change or mutations that are unique to every cancer patient and linking these findings to a targeted therapeutic regimen. This creates a major change in the way patients are being treated, not only for cancer but for many other diseases. The treatment is more effective with lesser side effects for patients as compared to generalised treatment approaches. More drugs are being triaed for different cancer types with updates on international treatment guidelines being released at frequent intervals. Thus, personalised or precision medicine is now truly a standard of care, for most if not all types of cancers. Genomic testing of tumours is playing a crucial part in treatment, it helps in accurate diagnosis of many types of cancers, predictive in many instances and provides insight into tumour development and progression.

The rapid paced development that has taken place in the field of genomics and personalized medicine for the last 15 years is centered around the fact that the Human Genome Project was successful in mapping out the entire human genome, which comprises of 3 billion DNA base pairs and around 25,000 genes in every person.We now understand better about genes and chromosomes, and the pathologies related to the genetic makeup in humans. This has led to the development of new tools to obtain and analyze the genomic data from cancer biopsy samples. The next generation sequencers can analyze the whole genome regardless the number of genes. It can accurately detect an abnormality in one out of 3 billion base pairs in human DNA. Multiple samples can be analyzed simultaneously with a quick turnaround time and now at a cost that makes these tests practical and feasible in everyday clinical care. Furthermore, smaller amount of tumour samples is being utilized for genomic analyses. The next generation of instruments are also offering accurate detection of genetic abnormalities in liquid biopsies, which are comprised of miniscule amount of tumour DNA circulating in a patient’s blood. This in turn is helping physicians monitor tumour recurrence or progression after treatment.

While there are exciting developments in the oncology and non-oncology care through genomics, these are not without challenges for healthcare providers and public health, overall. The large amount of data produced through the genomic testing needs to be securely stored for prolonged periods. Challenges dealing with data privacy, ethical issues, modifications required in reimbursement models, patient and physician education and adoption, issues dealing with intellectual property, maintenance of effective and reliable standards of genomic testing are just to name a few. Nevertheless, genomic testing of patients is here to stay and despite its challenges, the interplay between personalized medicine and pharmacogenomics has given us tremendous hope and a formidable step towards conquering cancer.